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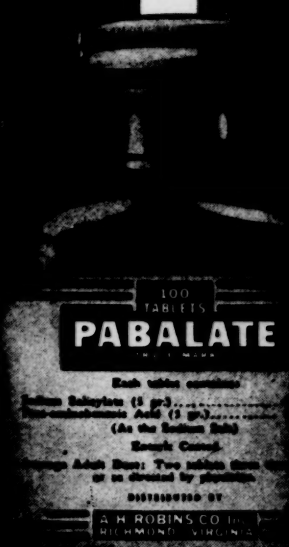
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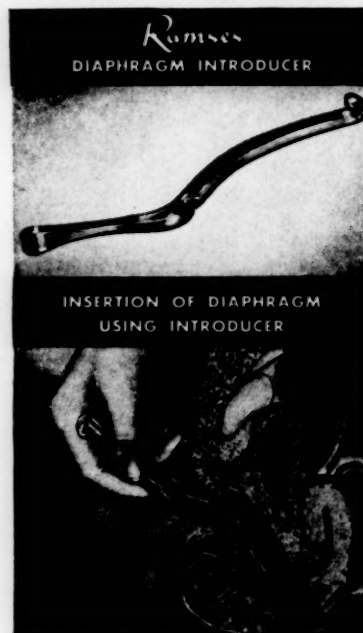
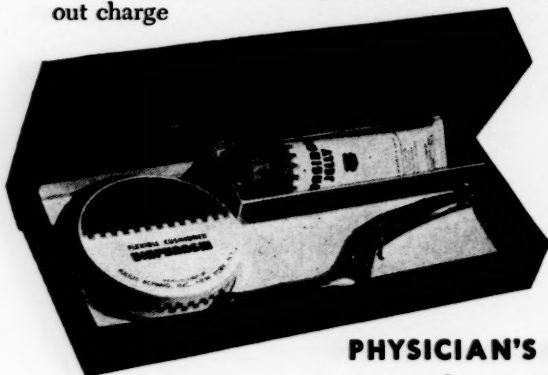
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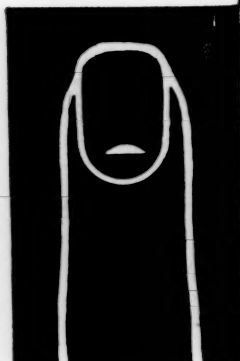
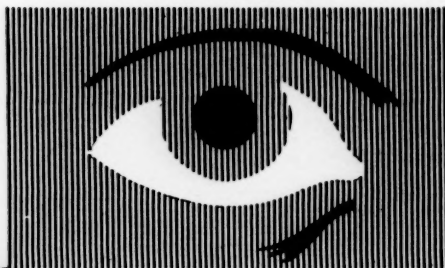
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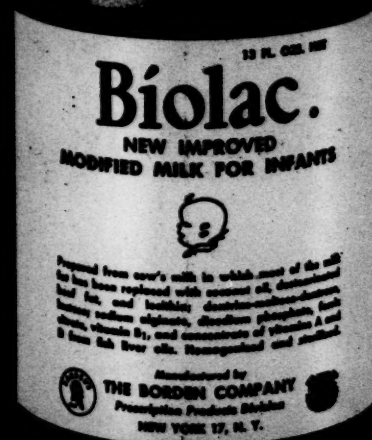
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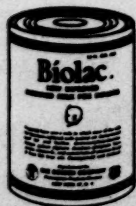
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BIBLIOGRAPHY: (1) Fishberg, A. M.: *Heart Failure*, 2nd ed., revised, Philadelphia, Lea & Febiger, 1946, p. 736. (2) Levine, S. A.: *Clinical Heart Disease*, 3rd ed., revised, Philadelphia, Saunders, 1947, p. 278. (3) *New and Nonofficial Remedies*, 1947, p. 304. (4) Reaser, P. B. and Burch, G. E.: *Proc. Soc. Exper. Biol. & Med.* **63**:543, 1946. (5) Modell, W., Gold, H. and Clarke, D. A.: *J. Pharm. & Exper. Therap.* **84**:284, 1945. (6) DeGraaf, A. C. and Nadler, J. E.: *J.A.M.A.* **119**:1006, 1942. (7) Wexler, J. and Ellis, L. B.: *Am. Heart J.* **27**:86, 1944. (8) *Conferences on Therapy: New York State J. Med.* **44**:280, 1944; **46**:62, 1946; **46**:69, 1946.

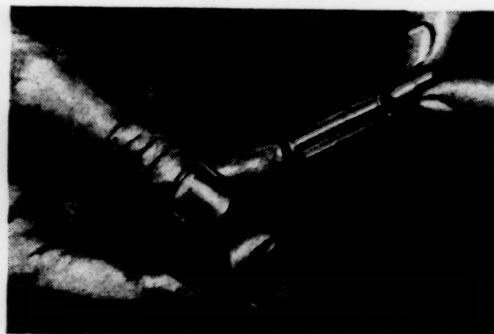
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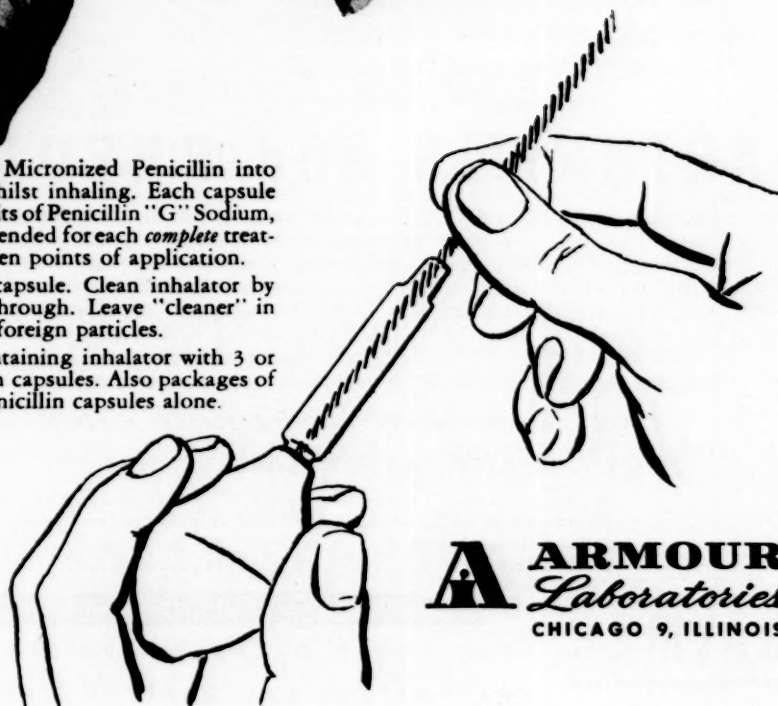
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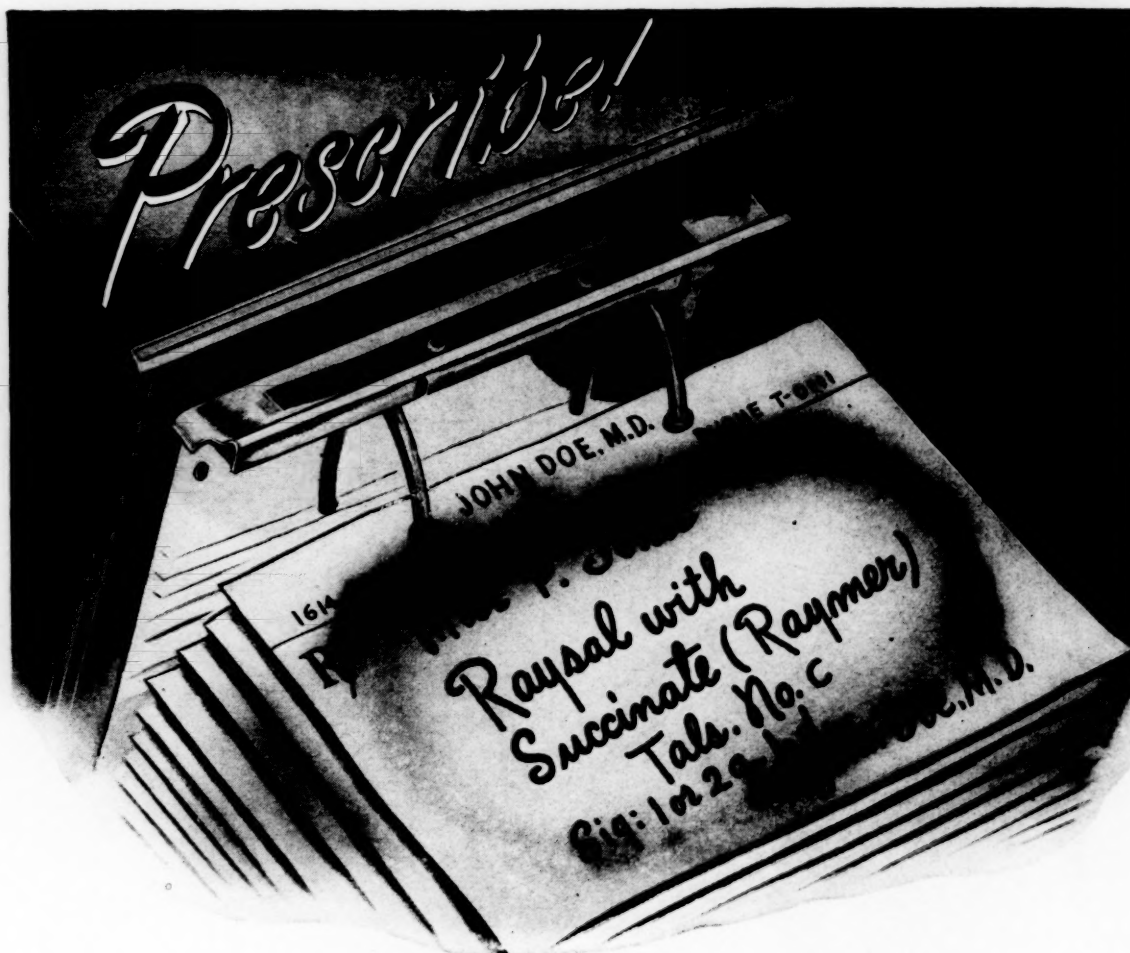
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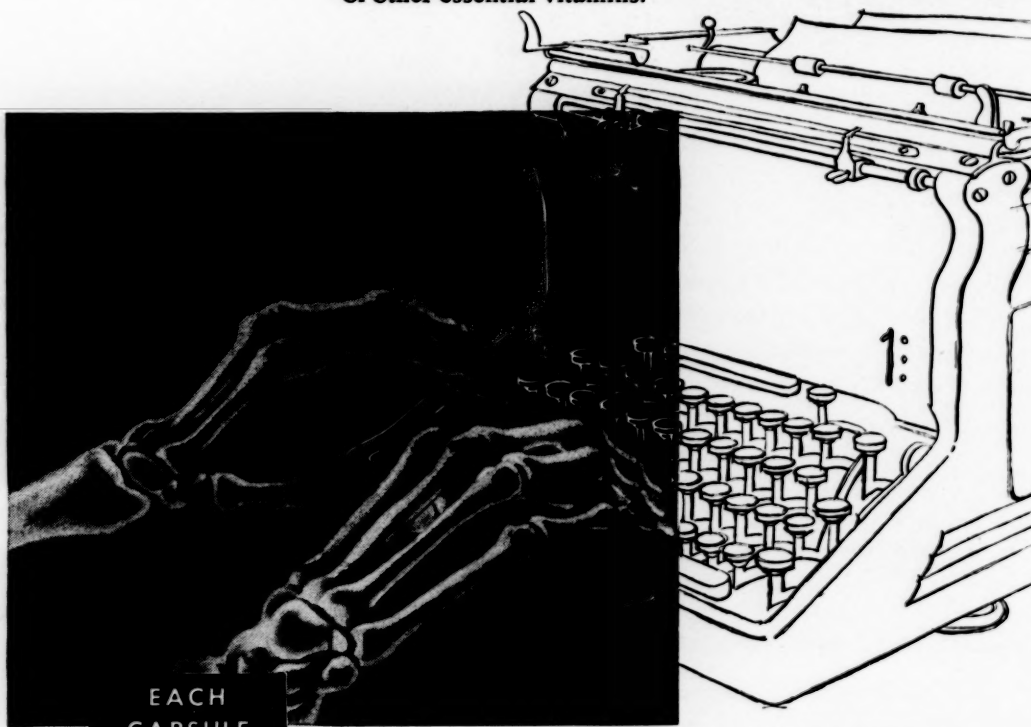
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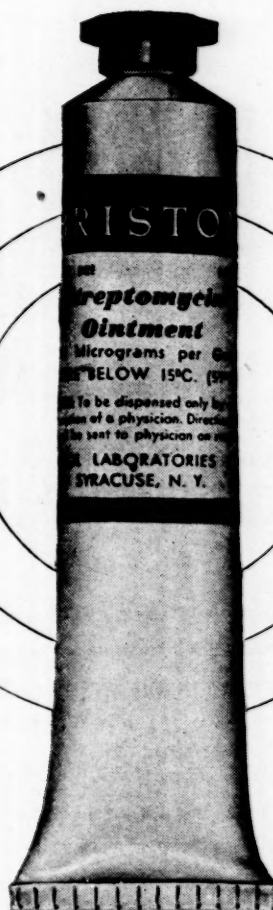
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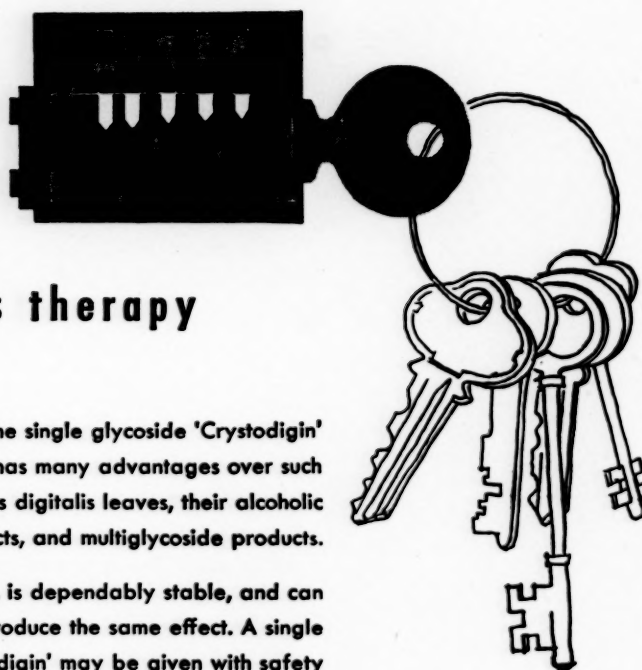
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(1) F. L. Meleney. Surg., Gynec. & Obst. 86:760 (June), 1948

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The American Journal of Medicine

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APRIL, 1949

No. 4

Editorial

New Antibiotics

WITHIN the past year three new antibiotics have been announced for the treatment of certain infections that have failed to respond to penicillin or streptomycin. They are chloromycetin, aureomycin (Duomycin) and bacitracin.

Great interest has been focused on chloromycetin,¹ especially in the treatment of rickettsial diseases (epidemic typhus, scrub typhus, Rocky Mountain spotted fever and Q fever) and typhoid fever. There seems to be little doubt that this new antibiotic is highly effective in all of the human rickettsial diseases that have been studied. The duration of the disease is definitely shortened following its use and the clinical course is changed in a striking manner within twenty-four to seventy-two hours after chloromycetin is started. Chloromycetin is effective when given by mouth and the side effects are minimal.

In typhoid fever the results of treatment with chloromycetin have been extremely impressive. When treatment was started in the first two weeks of the disease, the average duration of fever was only 3.5 days after treatment was started. The average duration of the febrile course of the disease in the treated cases was approximately 12.5 days, whereas in a control group of patients who received no chloromycetin the average duration of the disease was thirty-five days. The difference in the

duration of the disease in these two groups therefore was very significant.

In addition to the rapid decrease in the fever there was evidence of improvement in the general condition of the patient and a decrease in the signs of intoxication within twenty-four hours. The bacteremia was cleared permanently in eight of ten cases. Chloromycetin in the doses that were used did not prevent relapses nor complications such as perforation and hemorrhage, even in the afebrile period of the disease. Relapses responded to further chloromycetin therapy.

It is plain, then, that chloromycetin alters the clinical course of typhoid fever but with the dosage schedules that have been used so far relapses and complications even during the afebrile stage of the disease following treatment have not been prevented. Optimal dosage schedules should be explored further.

The *in vitro* bacterial spectrum shows that chloromycetin is effective in small concentrations against many gram-positive and gram-negative organisms. Moderately high concentrations are required for certain gram-negative bacilli and mycobacteria. It is ineffective against rabbit syphilis, protozoa and various fungi. It has been effective against the growth of some strains of psittacosis in eggs and mice. It does not have any effect against pneumococcal infections nor against various experimental virus infections in mice. It is quantitatively inferior to streptomycin against many bacterial infections in mice.

So far as the information goes at present

¹ WOODWARD, T. E., SMADEL, J. E., LEY, H., JR., GREEN, R. and MANKIKAR, D. S. Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever. *Ann. Int. Med.*, 29: 131, 1948.

the greatest field of usefulness for chloromycetin would appear to be in the treatment of rickettsial infections and in typhoid fever. Further clinical studies are needed to define its place in the treatment of other bacterial infections and in virus infections.

Aureomycin² has been used with great success in the treatment of human cases of acute brucellosis, lymphogranuloma venereum, Rocky Mountain spotted fever, Q fever and in typhus fever. Some patients with urinary tract infections that were resistant to penicillin and streptomycin have responded favorably to aureomycin (*Bacillus coli*, *aerogenes*, *Bacillus paracolon*, *Streptococcus faecalis*). There is evidence from the study of experimental infections in animals that rickettsial infections and the psittacosis viruses respond favorably to its action. Bacterial infections of the conjunctivae caused by staphylococci, pneumococci and *Hemophilus influenzae*, diplobacillus of Morax-Axenfeld and Friedländer's bacillus have been reported to respond favorably following the local use of aureomycin (aureomycin borate, 0.5 per cent concentration). Inclusion conjunctivitis, follicular conjunctivitis and herpes simplex of the cornea also have cleared under treatment.

The favorable response of some patients with primary atypical pneumonia following aureomycin has been very striking. The temperature declines and the signs of intoxication regress in a period of thirty-six to seventy-two hours after the drug has been given. This is of great interest since

up to the present time aureomycin has not been found to be effective in any proved virus infection. It is also ineffective in *Proteus vulgaris* and *Pseudomonas aeruginosa* infections but its effect in *Salmonella* and typhoid infections is questionable.

In brief, then, both aureomycin and chloromycetin have proved to be highly effective in rickettsial infections. In addition chloromycetin has a striking effect in typhoid fever whereas the effect of aureomycin in this disease is questionable. Aureomycin influences lymphogranuloma venereum, acute brucellosis and some cases of primary atypical pneumonia and urinary tract infections in a favorable sense and it has been used in penicillin- and streptomycin-resistant bacterial infections that are sensitive to aureomycin.

Bacitracin³ has been useful in the treatment of wound and ocular infections that are resistant to penicillin. Due to the fact that it has been difficult to prepare bacitracin that is free of renal toxic factor, its use at present is limited to the treatment of local infections with solutions or ointments.

It can be said that great advances are being made every year in the war against infections. One infection after another can now be treated with anti-infective agents that were non-existent ten years ago. It is not too much to expect that the search for new agents now in progress will yield additional remedies that will aid in the treatment of infections that cannot be controlled at the present time.

CHESTER S. KEEFER, M.D.

² Aureomycin—A New Antibiotic. (A series of sixteen articles by forty-three authors.) *Ann. New York Acad. Sc.*, 51: 175-342, 1948.

³ MELENEY, F. L., ALTEMEIER, W., LONGACRE, A. B., PULASKI, E. J. and ZINTEL, H. A. The results of the systemic administration of the antibiotic, bacitracin, in surgical infections. A preliminary report. *Ann. Surg.*, 128: 714-731, 1948.

Clinical Studies

Aureomycin in Typhus and Brucellosis*

VERNON KNIGHT, M.D.,† FRANCISCO RUIZ-SANCHEZ, M.D., AMADO RUIZ-SANCHEZ, M.D.
and WALSH McDERMOTT, M.D.
New York, New York

IN the summer of 1948 in the course of an investigation of the antimicrobial therapy of typhoid fever with various drugs, eleven patients with typhus‡ and five with brucellosis were treated with aureomycin. The studies were conducted in Mexico by a group of investigators from the University of Guadalajara and the New York Hospital-Cornell University Medical College. As a striking improvement occurred uniformly in the typhus and brucella infections immediately after the start of therapy, observations on these cases are reported at this time. The results of the typhoid study will be presented in a subsequent report.¹

TYPHUS FEVER

Clinical Material and Methods of Study. In Guadalajara typhus is a frequent cause of fever and is part of an endemic triad including brucellosis and typhoid fever. Official statistics are lacking, but an approximation of the local prevalence of typhus is supplied by the study of Ruiz-Sanchez and his associates² who found positive Weil-Felix agglutinations in 11.1 per cent of 704 specimens of serum submitted for other serologic testing. These investigators considered as positive only those tests in which agglutination occurred in a dilution of 1:50 or higher. With due consideration for the fact that the Weil-Felix test may remain positive for many months after a typhus infection, these data indicate that the disease is widespread in the

region. Murine typhus is the variety which occurs most frequently³ and the clinical manifestations of the Guadalajara disease are identical with those seen in the murine typhus of other localities.

The characteristic findings in the typhus infections studied included: high fever, headache, a spotted rash in the first week of illness, splenomegaly and various types of gastrointestinal disturbances. Leukopenia and relative bradycardia are not uncommon so that in this locality it is virtually impossible to differentiate the early stages of typhus from the much more prevalent typhoid fever. Prostration is usually less severe in the typhus infections, however, a distinction which is occasionally of value. Complications of the typhus are not described and the case fatality rate is extremely low. All of the ten cases treated in Mexico clinically resembled murine typhus. The New York Hospital case was exposed to the rickettsia of endemic (murine) typhus in a research laboratory and also clinically conformed to the picture of the Mexican cases.

The diagnosis of typhus was established in all ten of the patients treated in Mexico by demonstration of a significant rise in agglutination titer in the Weil-Felix reaction. The final titer was as low as 1:160 in only one of these cases while in the others the titers ranged from 1:640 to 1:3200. These results are presented in Table 1 arranged according to the day of the disease.

The only other specific diagnostic procedure obtained was the complement fixation test.*

* These tests were obtained through the courtesy of Doctor Herald Cox, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

‡ One of these patients was treated at the New York Hospital during the period of the Mexican investigation.

* From the Institute for the Experimental Study of Infections of the University of Guadalajara, Jalisco, Mexico, and the Department of Medicine of the New York Hospital-Cornell University Medical College, New York, N. Y. The study was aided in part by grants from: The Division of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service; the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York; and Charles Pfizer and Company, Brooklyn, New York.

† National Institutes of Health, U.S. Public Health Service, Postdoctorate Research Fellow.

The results of these tests are shown in Table II and are also arranged according to the day of disease. The titers observed indicate the presence of rickettsial antibodies in the majority of the cases, and in four the reaction was slightly greater against the rickettsiae of epidemic

last seven patients treated in the series, also adults, received 175 to 200 mg. per Kg. per day in equally divided doses at three-hour intervals. One of the patients received therapy for twenty-four hours only, four for thirty-six hours and two for a total of forty-eight hours. (Table III.)

TABLE I
WEIL-FELIX REACTION* ACCORDING TO DAY OF DISEASE

Patient	Day of Disease†									
	4	6	8	10	12	14	16	18	20	22
R. Gon.....	0	0	1:320	1:800					
W. Ro.....						..	1:640	1:3200	1:3200
P. De.....			0		1:160	..	1:160			
F. Mo. (NYH).....				0	0					
L. Av.....				1:40	1:80	..	1:320	1:640		
P. Os.....				1:320	1:640					
R. Gom.....		1:640	1:640							
G. He.....			1:80	1:160	1:640					
E. Al.....		0		1:640						
A. Nu.....		1:80	1:320		1:1920					
T. Go.....			1:640		1:1920					

* *Proteus* OX 19 antigen.

† Odd days reported on next day.

typhus. The patient treated in the New York Hospital had several Weil-Felix tests with no agglutination, but a complement fixation test was reported in which titers of 1:256 or greater against both endemic and murine antigens were observed. Unfortunately, however, it was not possible in any of the cases to obtain rickettsial agglutination tests in order to determine whether the individual infections treated were murine or epidemic typhus. For the reasons presented above it is believed that all of the group were infected with the murine variety.

Examinations of the urine and determinations of the total leukocyte and erythrocyte counts and the concentration of hemoglobin were made before and after therapy. The results were consistent with the diagnosis of typhus and revealed no evidence of aureomycin toxicity.

Aureomycin was administered orally in divided doses in 100 and 250 mg. capsules. The first three patients treated were adults who received 6 Gm. the first day and 4 Gm. daily for five additional days (approximately 53 to 89 mg. per Kg. per day). The New York Hospital patient received 6 Gm. daily for three days and 4 Gm. daily for the four succeeding days (approximately 90 mg. per Kg. per day). The

No determinations of the concentrations of aureomycin in the blood were made in any of the cases.

Antimicrobial therapy was started on or before the eighth day of the disease in eight patients, and on the tenth, twelfth and sixteenth day in the remainder. A summary of the data concerning dosage and clinical course is presented in Table III.

RESULTS

In every instance the institution of therapy was followed by a remarkable improvement in all of the signs and symptoms of the typhus. The change was clearly evident in the first twenty-four hours in all the patients although in four the fever persisted longer and in one case for as long as seventy-two hours. Even in these four patients, however, the temperature was never elevated to more than 38°C. after the first day of chemotherapy. Headache and gastrointestinal symptoms disappeared overnight and the rash, when present at the start of therapy, faded completely in two to three

days. The duration of fever after therapy may be seen in Table III and Figure 1.

Other than occasional vomiting of the medication no significant toxic effects were observed in any of these patients. In no instance was the vomiting of sufficient severity to cause therapy to be discontinued.

between three and six months following the treatment with aureomycin.

BRUCELLOSIS

Clinical Material and Methods of Study. Five young adults with brucellosis were treated with aureomycin. Four were acutely febrile at the

TABLE II
COMPLEMENT FIXATION * ACCORDING TO DAY OF DISEASE

Patient	Antigen	Day after Onset								
		6	8	10	12	14	16	18	20	22
R. Gon.	Epidemic	1:32†	..	1:32						
	Murine	1:16	..	1:16						
	Anti-comp.	1:8	..	1:8						
W. Ro.	Epidemic	1:32	1:64
	Murine	1:16	1:32
	Anti-comp.	1:4	1:8
P. De.	Epidemic	1:16	..	1:32		
	Murine	1:8	..	1:16		
	Anti-comp.	1:4		
F. Mo. (NYH)	Epidemic	1:256‡		
	Murine	1:256‡		
L. Av.	Epidemic	0				
	Murine	0				
P. Os.	Epidemic	1:16				
	Murine	0				
R. Gom.	Epidemic	not tested not tested								
	Murine									
G. He.	Epidemic	0					
	Murine	0					
E. Al.	Epidemic	not tested not tested								
	Murine									
A. Nu.	Epidemic	not tested not tested								
	Murine									
T. Go.	Epidemic	0					
	Murine	1:4					

* The writers are indebted to Dr. Herald Cox, Lederle Laboratories Division of American Cyanamid Co., for the performance of these tests.

† Each value represents titers interpreted as 3 + or greater.

‡ Or higher.

Relapse of the infection has not been observed. The subsequent course of the group has been followed for periods ranging

start of therapy and one was afebrile with a chronic form of the disease. In the febrile group the diagnosis was established by the demonstra-

tion of bacteremia in two cases and by significant rise in antibody titer in the two others. The presence of the chronic infection was established by means of serum agglutination tests and by a blood culture obtained in an outside laboratory ten days before the start of treatment.

TABLE III
FEBRILE COURSE AFTER START OF AUREOMYCIN THERAPY
IN TYPHUS

Patient	Day after Onset Treatment Begun	Dosage Regimen		Hours Febrile* after Therapy
		Duration of Treatment	mg./Kg./day	
R. Gon.	4	6 days	53	48
W. Ro.	16	6 "	57	36
P. De.	6	6 "	89	24
F. Mo. (NYH)	10	7 "	90	72
L. Av.	8	48 hours	200	24
P. Os.	12	48 "	200	24
R. Gom.	7	36 "	175	36
G. He.	8	36 "	200	24
E. Al.	6	36 "	200	48
A. Nu.	6	33 "	177	48
T. Go.	8	24 "	200	24

* 37.5°C. or greater.

The results of the laboratory tests obtained in these patients are presented in Table iv. Examinations of the blood and urine before and after therapy disclosed no evidences of toxicity or findings inconsistent with the diagnosis of brucellosis.

All of the four patients with acute infections presented the characteristic clinical manifestations of brucellosis. In addition, one patient (T. F.) had definite signs and symptoms of

meningeal involvement. The four acutely ill patients had been febrile for nine, twenty-six, sixty and ninety-five days, respectively, before treatment. The patient with chronic infection had been ill for two years and exhibited symptoms of malaise, general poor nutritional state,

TABLE IV
LABORATORY DIAGNOSIS OF BRUCELLOSIS

Patient	Serum Agglutination	Blood Culture
	(range)	
J. G.	1:80 to 1:640	+†
T. F.*	1:640 to 1:640	+
A. C.†	1:80 to 1:320	0
C. M.	1:180	+
G. V.	1:500	+

* This strain reacted as *B. melitensis* in the dye differentiation and sulfide production tests.

† Following first serum agglutination reported, this patient received brucella antigen as therapy.

‡ During relapse.

joint pains and occasional episodes of evening temperature elevation.

Aureomycin was employed in a manner similar to that used in the treatment of murine typhus. In general, the regimen consisted of 6 Gm. of drug the first day in divided doses and 4 Gm. daily thereafter for an additional five days. One patient (C. M.) received 9.5 Gm. daily for seven days and the patient with meningeal involvement received treatment for only three and one-half days before leaving the hospital against advice. (Table v.)

RESULTS

The results following therapy in the febrile cases were striking. In each case

TABLE V
CLINICAL COURSE IN TREATED BRUCELLOSIS

Patient	Days Ill at Start of Treatment	Temperature*	Immediate Clinical Result	Days Febrile after Start of Treatment	Follow-up
J. G.	9	39.0	Marked improvement	3	Relapse after 42 days
T. F.	26	39.0	Marked improvement	4	Asymptomatic—3 months
A. C.	95	39.3	Marked improvement	4	Asymptomatic—4½ months
C. M.	60	38.5	Marked improvement	4	Relapse after 15 days
G. V.	2 years	Normal	No change	..	No change

* Highest temperature on the day before therapy was started.

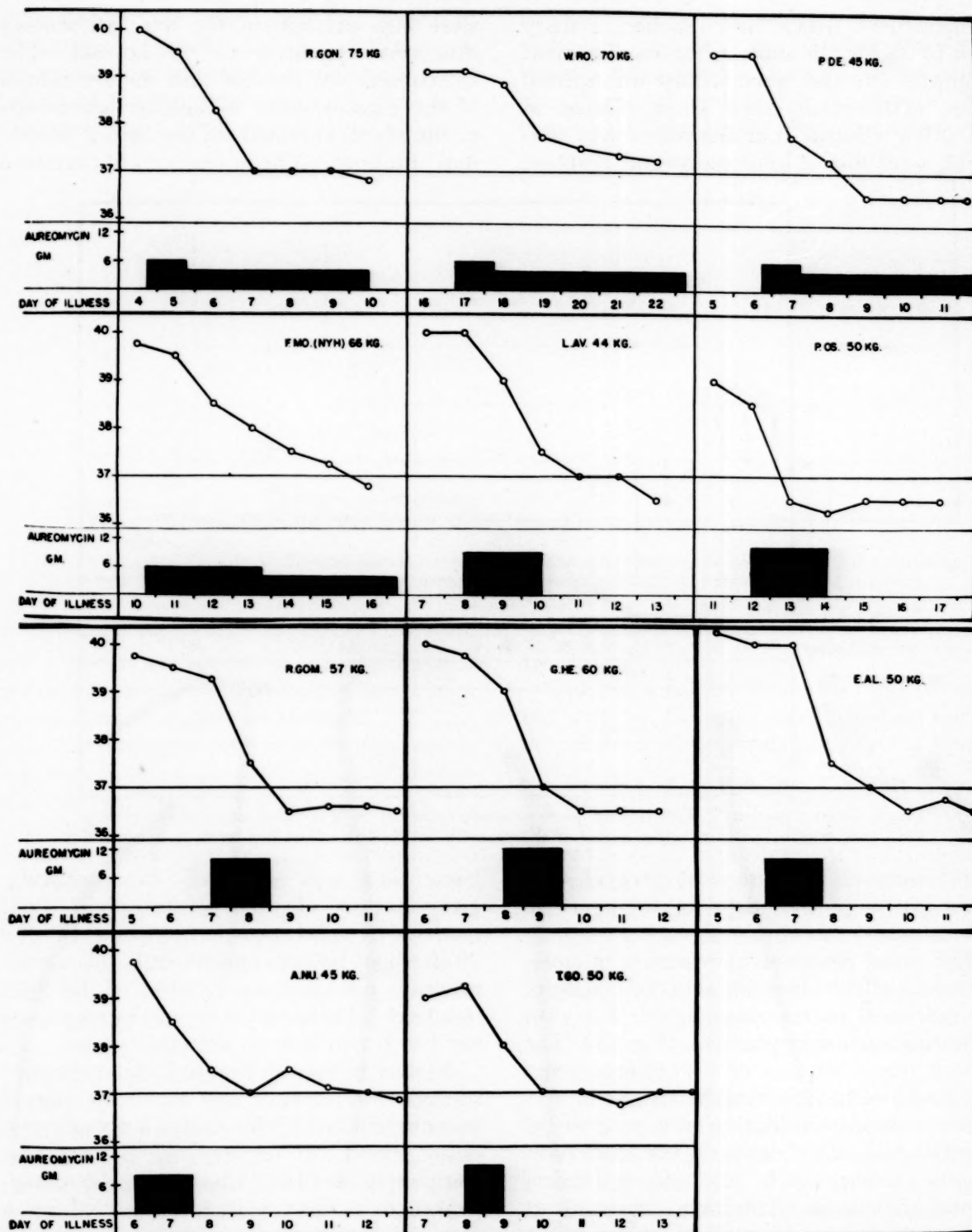


FIG. 1. Maximal daily temperatures after aureomycin treatment in typhus fever, showing immediate and uniform return of the temperature to normal.

temperatures which had reached a daily high of 38.5°C. or more prior to treatment promptly fell and were within the normal range within four days. Improvement in the other clinical manifestations was also rapid, with loss of joint pains and malaise,

were also present on the left. All sensory functions appeared to be normal. The spleen was not palpable and the remainder of the examination, including fluoroscopy of the chest, revealed no significant abnormal findings. The presence of brucella

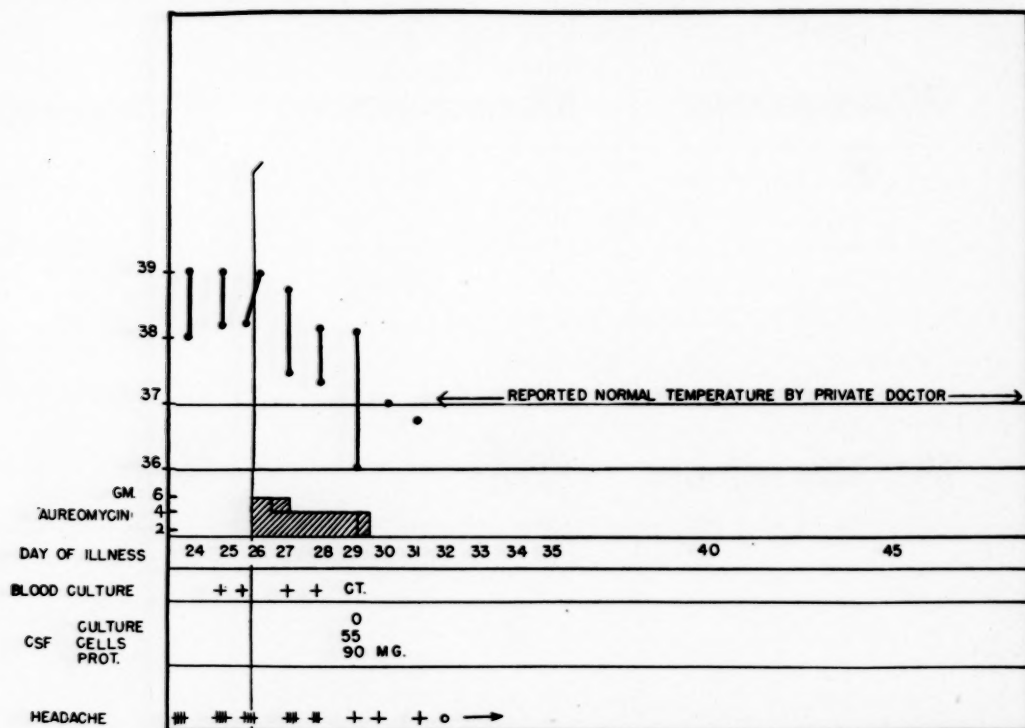


FIG. 2. Chart of patient T. F., who had acute meningo-encephalitic brucellosis and who was treated with aureomycin, showing improvement after treatment with return of the temperature to normal.

and return of appetite and general well being within a few days of the start of antimicrobial therapy.

The most impressive evidence of antimicrobial effect observed was the course of the infection in the patient (T. F.) with acute meningo-encephalitis. (Fig. 2.) The patient was a woman of twenty-four years who had fever and joint pains for one month before normal termination of a pregnancy. Immediately after delivery her condition became worse, with high fever, severe frontal headache, vomiting, generalized aches and pains and stiffness of the neck. Physical examination seven days postpartum revealed moderately severe bilateral papilledema and nuchal rigidity. Hyperreflexia was present and most marked on the left. Hoffman's and Babinski's signs

bacteremia was repeatedly demonstrated. Examination of the cerebrospinal fluid revealed a total protein concentration of 90 mg. per 100 cc. and 55 cells (all mononuclear) per cu. mm. Culture of the fluid in a liver infusion medium and in trypticase soy broth revealed no growth.

As may be seen in Figure 2, defervescence started soon after the first administration of aureomycin and by the end of a seventy-two hour period of therapy the patient was completely afebrile. Moreover, the disappearance of fever was accompanied by a marked diminution of the evidences of central nervous system involvement. The nuchal rigidity and the abnormal reflex responses disappeared promptly and the papilledema was greatly diminished when the patient left the hospital on the fourth

day of treatment. The intensity of the headache steadily decreased and this symptom disappeared entirely during the first week at home. The patient has remained completely asymptomatic during the four months since the cessation of antimicrobial therapy.

preceding antimicrobial therapy and conceivably was related to it. With the disappearance of fever the patient improved rapidly although it was several weeks before she felt entirely well and asymptomatic. The remission of her disease has been maintained

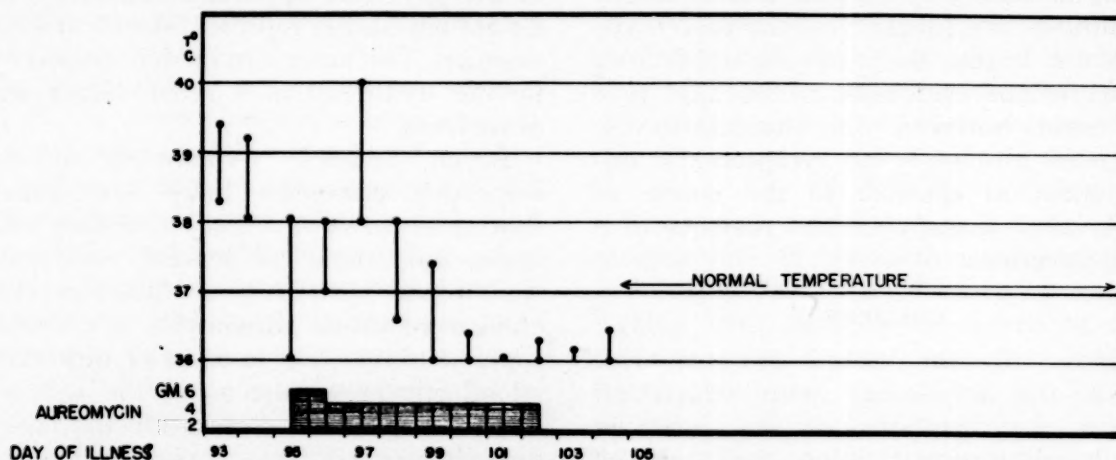


FIG. 3. Chart of patient A. C., who had acute brucellosis and who was treated with aureomycin, showing abrupt rise in temperature at the forty-eighth hour of treatment followed by complete clinical remission.

It should be noted that despite the immediate clinical improvement the bacteremia persisted for at least forty-eight hours after aureomycin therapy was started.

A phenomenon of possible significance was noted during the early period of chemotherapy of a twenty year old female (A. C.) who had been acutely ill with brucellosis for ninety-five days. When aureomycin was instituted, her principal symptoms consisted of weakness, weight loss, malaise, joint pains, night sweats, dizzy spells and tachycardia. Her temperature ranged daily from 38° to 40°C. throughout the pretreatment period except for a few three- to four-day afebrile intervals.

As may be seen in Figure 3, approximately thirty-six hours after the start of treatment the patient experienced an abrupt elevation of temperature to 40°C. accompanied by a shaking chill. The temperature remained above 39.5°C. for a period of approximately twelve hours and then fell during the ensuing twenty-four hours to the normal range where it remained thereafter. This episode was in contrast to the course of her infection in the days immediately

during a follow-up period of approximately five months.

The third patient was a twenty-one year old male (J. G.) who was started on aureomycin therapy after only nine days of illness. Defervescence occurred during the first seventy-two hours of antimicrobial therapy and was accompanied by complete disappearance of all symptoms. After an afebrile period of forty-two days, however, fever and arthralgia recurred and was accompanied by bacteremia due to brucella. The reinstitution of aureomycin was again followed by a remission of all signs of the infection and the patient has been entirely well during the subsequent two and one-half months.

The fourth patient (C. M.) received a larger dose of drug than the first three cases. Her clinical response, however, closely resembled that of J. G. except that ninety-six hours were required for defervescence. Fifteen days following cessation of therapy a relapse occurred, with fever, bacteremia and a return of symptoms. Because the patient moved from the city, retreatment was not possible.

The patient with chronic brucellosis was afebrile at the start of therapy and showed no alteration of symptoms attributable to therapy. Pain and stiffness in both knees persisted after treatment. A feeling of malaise with poor appetite was present during the follow-up interval of three weeks. As cultures were negative at the time treatment was begun, there was no satisfactory means for the evaluation of therapy. It is of interest, however, that the patient experienced absolutely no symptomatic improvement in contrast to the course of events after therapy in the patients with acute infections.

COMMENT

Typhus. In the eleven patients with typhus the uniformity with which all clinical manifestations of the infection rapidly disappeared after the start of aureomycin therapy affords evidence that the observed remissions were drug-induced. Recovery by "crisis" may occur in typhus fever but is unusual.⁴ In contrast, in the aureomycin treated patients recovery by "crisis" occurred uniformly. The average duration of fever after the start of therapy was only 1.7 days, and this appeared not to vary greatly whether the treatment was started on the fourth, seventh, eighth, twelfth or sixteenth day of illness. Because of the variable time at which treatment was started no precise comparison can be made with the natural course of the untreated disease.

In Guadalajara untreated typhus usually runs a febrile course for approximately two weeks³ but fever may persist for twenty or more days. In 180 cases of murine typhus studied at Charity Hospital, New Orleans, by Stuart and Pullen⁵ the average febrile period was 15.6 days, while in Woodward's careful study of the length of the febrile period in fourteen cases of murine typhus in North Africa⁴ the average febrile period was twelve days.

From the above data it appears that the administration of aureomycin exerted a prompt and impressive effect upon the

course of infection in the eleven patients with typhus. It is also impressive that no relapses were observed despite the fact that in seven patients the total period of antimicrobial therapy was limited to only one or two days. Although these short periods of therapy were apparently effective, they do not necessarily represent the ideal dosage regimen. The latter can be determined only by the treatment of a much larger series of patients.

Payne,⁶ Smadel,^{7,9} Woodward⁸ and their respective associates have demonstrated that chloromycetin exerts a striking effect upon the course of several varieties of typhus and spotted fever. Whether either chloromycetin or aureomycin is materially superior to the other in terms of antirickettsial effectiveness must await the results of direct comparative studies. On the basis of the evidence available at present, however, it appears that both drugs are powerful antirickettsial agents which exert a considerably greater effect than para-aminobenzoic acid, the most satisfactory of the antirickettsial agents hitherto available.⁹

Brucellosis. Remissions of the acute manifestations of brucellosis may occur with such abruptness and with sufficient frequency that it is difficult to evaluate antimicrobial agents in the treatment of this infection. Consequently the fact that the four patients in the present study all experienced a complete remission of their acute disease soon after the start of aureomycin therapy can be considered only as suggestive of a drug effect. The course of events in the patient with meningo-encephalitis and bacteremia, however, affords much more impressive evidence of drug effect. Meningo-encephalitis occurs infrequently in brucellosis but represents a serious complication. Of two cases reported by Huddleson¹¹ one died after a protracted illness and the other continued to present abnormal neurologic signs for more than six months before gradual improvement was first observed. In contrast, in the aureomycin treated patient with meningo-encephalitis, defervescence and dramatic symptomatic improvement ap-

peared within forty-eight hours of the start of chemotherapy and complete recovery occurred during the subsequent week. It is believed that such a rapid recovery from acute meningo-encephalitis with bacteremia would have been most unlikely in the natural course of the infection and presumably represents an effect attributable to the aureomycin.

As noted above, in one patient (A. C., Fig. 3) the onset of defervescence was immediately preceded by an intensification of the evidences of infection manifested by a chill, a sudden elevation in temperature and tachycardia with bothersome cardiac palpitation. These symptoms appeared approximately forty-eight hours after the start of aureomycin therapy, were of only moderate severity and may well have merely represented daily variations in the intensity of the infection. The incident is worthy of mention, however, because of the observation of Spink and Castaneda and their associates¹² that certain of their patients with acute brucellosis experienced rather alarming intensification of the infection during the first day of aureomycin therapy. In the other three patients with acute brucellosis in the present series (two of whom were bacteremic) the onset of defervescence was not preceded by intensification of the illness.

As with the typhus patients, considerably more experience with the aureomycin treatment of brucellosis must be acquired before the most satisfactory dosage regimens are defined. The patient with meningo-encephalitis experienced a remission which has been sustained for four months after only three and one-half days of antimicrobial therapy. Nevertheless, the appearance of a febrile relapse in two patients fifteen and forty-two days after a one-week period of aureomycin therapy indicates that a longer total period of therapy will probably prove to be advisable.

SUMMARY

The administration of aureomycin* to eleven patients with typhus (presumably

* The aureomycin used in this investigation was sup-

murine) was followed in every instance by prompt defervescence and complete recovery. No instances of relapse were observed despite the fact that in seven cases the total period of antimicrobial therapy was limited to forty-eight hours or less.

In four patients with acute brucellosis, one of whom had meningo-encephalitis, a similar prompt disappearance of the manifestations of the infection occurred soon after the start of aureomycin therapy.

ADDENDUM

Since this material was submitted for publication, an additional eight patients with typhus fever have been successfully treated with aureomycin. Seven of these patients were treated with oral dosages ranging from 100 to 160 mg. per Kg. per day, for intervals of thirty-six to forty-eight hours. These patients all showed rapid improvement after therapy in every way as satisfactory as that described for the previous patients. Five of these patients had continuously normal temperatures within thirty hours after starting therapy while the two remaining individuals, although greatly improved, showed slight elevations of temperature on the third day after starting treatment. In one of these cases this slight rise in temperature was associated with profuse epistaxis which responded to local treatment. Convalescence was otherwise uneventful.

One patient in the eighth day of her illness received aureomycin intravenously. She was given doses of 200 mg. at approximate eight-hour intervals during the first day and at twelve-hour intervals during the second day. Improvement was rapid so that by the time the last dose was administered she was essentially asymptomatic and permanently afebrile. Convalescence was entirely uneventful and there was no local or systemic evidence of reaction to therapy.

Other patients were treated with lower oral dosages in an attempt to discover a

plied through the courtesy of Doctor Benjamin Carey, Director, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

subeffective dose. One such patient, treated with 25 mg. per Kg. per day for thirty-six hours, showed appreciably less benefit from therapy than those receiving larger doses. From these observations it appears that the lowest fully effective dose may lie somewhere between 50 and 100 mg. per Kg. per day for a short interval of therapy.

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Effect of Streptomycin Therapy on the Bacterial Flora of the Throat*

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SEVERAL investigators have reported that bacteria can develop resistance to streptomycin rapidly and to a high degree either in artificial culture media or during streptomycin treatment of an infectious process in man. This sudden development of resistance is presumed to result from the appearance of streptomycin-resistant variants which arise by mutation in the bacterial population.

With one exception,¹ the clinical reports seem to indicate that the streptomycin-resistant strains thus far recovered are analogous to the type A variant described by the authors and so designated to distinguish them from a second variant designated type B.² Both types have in common the ability to grow in high concentrations of streptomycin but are distinguished by the fact that the type A variant can multiply in the absence of streptomycin whereas type B requires streptomycin for its growth *in vitro* and *in vivo*.

Variants of both types have been found to arise in cultures of sensitive bacteria during their initial exposure to streptomycin when heavy seedings are spread on agar plates containing appropriate concentrations of the drug. They have been isolated from all of eighteen strains of meningococcus and also from a number of other bacterial species including *Aerobacter aerogenes*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas pyocyanea*, *Salmonella* and *Staphylococci*.³ These findings have been confirmed by Kushnick, Randles, Gray and Birkeland,⁴ by Paine and Finland,⁵ by Yegian and Budd⁶ and by Rake.⁷

The question naturally arises whether the

streptomycin-dependent variants occur in nature or only under the artificial conditions of laboratory experimentation. A search for type B variants was therefore made in animals and in patients undergoing treatment with streptomycin.

ANIMAL EXPERIMENTS

Streptomycin* in large doses was administered to normal mice and rabbits for periods up to three weeks. The mice received 2,000 micrograms twice a day subcutaneously or orally and the rabbits 50,000 micrograms once a day intravenously. All the animals remained healthy. From time to time an animal was sacrificed and cultures were made of the heart's blood, pharynx, large bowel and spleen onto media containing 400 micrograms of streptomycin per cc.

RESULTS

Streptomycin-resistant organisms were plentiful in the large bowel of both normal and treated mice and rabbits. During the second week of treatment streptomycin-dependent organisms began to appear. Their maximal incidence was estimated to be about 10 per cent of the micro-organisms which grew on streptomycin-containing media. At the beginning of the experiment pharyngeal cultures of the mice were negative on streptomycin media but became

* Preparations of streptomycin were supplied by the Antibiotics Study Section of the National Institute of Health, U. S. Public Health Service; the Division of Penicillin Control and Immunology, Food and Drug Administration; Abbott Laboratories; Commercial Solvents Corporation; Eli Lilly & Company; Merck & Company; Chas. Pfizer & Company; E. R. Squibb & Son and Upjohn Company.

* From the Department of Medicine, University of Chicago, Chicago, Ill. This investigation was undertaken and supported jointly by the U. S. Navy, Office of Naval Research, and the University of Chicago.

positive on the eleventh day and continued so until the end of the experiment. The cultures always contained some streptomycin-dependent micro-organisms although ordinary streptomycin-resistant organisms predominated.

Hearts' blood and spleen cultures remained negative throughout the experiment. The varieties of micro-organisms encountered in the pharynx and bowel differed in only one respect from those which make up the normal flora of these sites. There was an unusually high incidence of yeasts which constituted a large proportion of the streptomycin-dependent variants.

CULTURES ON PATIENTS

Cultures on streptomycin-containing media⁸ were made of the throats of patients undergoing treatment with streptomycin. The posterior pharyngeal wall was swabbed with two applicators. One swab was used to inoculate a blood (5 per cent defibrinated sheep's blood) agar plate containing 200 micrograms of streptomycin per cc. and the other a plate containing 400 micrograms of streptomycin per cc. The plates were incubated and examined at the end of twenty-four, forty-eight and seventy-two hours at which times the numbers of colonies were recorded. A culture was considered positive when five or more colonies were visible at forty-eight hours. The amount of growth appearing on the two plates containing 200 and 400 micrograms per cc. was approximately the same.

Representative cultures were studied in detail in order to determine whether the colonies were type A or type B variants. Single colonies were picked and subcultured onto both ordinary blood agar and onto media containing 100 micrograms of streptomycin per cc. Smears were stained by Gram's method and examined microscopically.

Additional cultures were taken from a number of throats which had been found to yield heavy growth in order to estimate what proportion of the total bacterial population was streptomycin-resistant or dependent. The throat was swabbed in the usual way and the swab rinsed in 2 cc. of broth from which a series of two-fold dilutions was made. Equivalent inocula were cultured in duplicate onto ordinary blood agar and blood agar containing 200 micrograms of streptomycin

per cc. and spread by means of glass beads as described in an earlier publication.²

The first series of cultures was made on patients in the Albert Merritt Billings Hospital of the University of Chicago. They included patients receiving streptomycin for the treatment of tuberculosis, ulcerative colitis, brucellosis or urinary tract infections and surgical patients being treated with streptomycin as a prophylactic measure. Those with pulmonary tuberculosis had been treated with streptomycin for a number of weeks before the first cultures were made. Many of the others, however, were followed from the time streptomycin therapy was begun and cultures were made daily until they became strongly positive.

The patients were given streptomycin intramuscularly in doses of 1.0 to 3.0 Gm. per day except those with colitis who took 4 Gm. per day by mouth. Some of the patients received penicillin and/or one of the sulfonamide drugs as well as streptomycin.

Control cultures were made on 157 members of the staff, students, laboratory and clerical personnel; on ninety-nine nurses and ward attendants and on seventy patients who were not receiving streptomycin.

In order to supplement our series of cultures on streptomycin-treated patients a survey was made of 114 patients undergoing streptomycin therapy in the Chicago Municipal Tuberculosis Sanitarium.* With eight exceptions all of the patients were receiving only 0.5 Gm. a day or 0.75 Gm. a day if their weight exceeded 70 Kg. The eight exceptions were patients treated with 1.0, 1.5 or 2.0 Gm. per day, and in the final tabulation they are included in the Billings series of patients. The patients in the M.T.S. series had been treated with streptomycin from three days to forty-five weeks. The cultures were taken as just described except that a single swab was used to inoculate a single plate containing 200 micrograms of streptomycin per cc.

RESULTS

Billings Series. The throat cultures of all but one of sixty-one patients in this series became positive. Cultures of fifty-five of them showed very heavy growth on streptomycin-containing media, indicating the presence of large numbers of streptomycin-

* The authors are indebted to Dr. George C. Turner, Superintendent of The Chicago Municipal Tuberculosis Sanitarium, for the opportunity to make these cultures.

resistant micro-organisms in the pharynx. Figure 1 presents the results of individual cultures on twenty-four patients who were followed from the beginning of streptomycin therapy or shortly thereafter. It will be seen that all of these cultures became positive by the thirteenth day.

taken from the third to the eighth day of streptomycin therapy. The bacteria on these plates included a *Staphylococcus albus* and a hemolytic *Staphylococcus aureus*.

We do not know when resistant bacteria appeared in the throats of the other thirty-

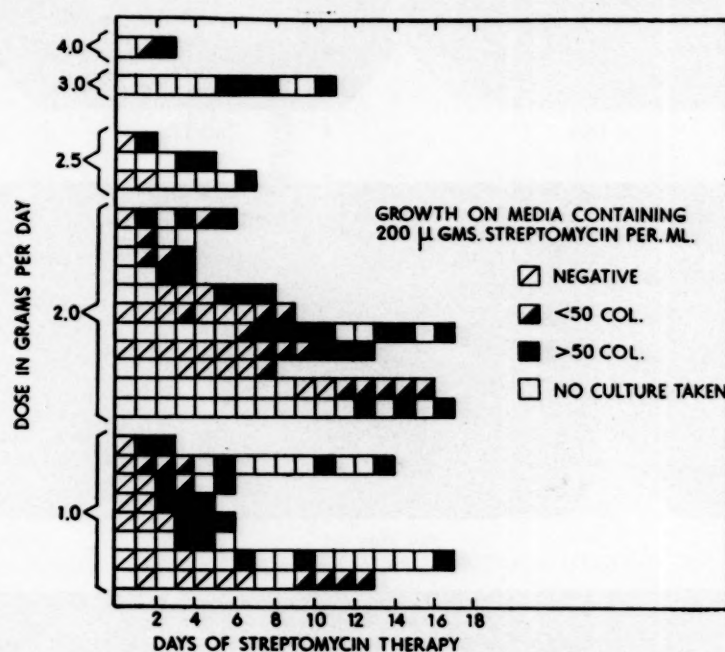


FIG. 1. Results of serial throat cultures in twenty-four patients receiving streptomycin.

Figure 2 illustrates the rate at which streptomycin-resistant bacteria appear in the throats of such patients by showing a series of daily cultures taken on two typical patients. Patient PG was a seventeen-year old boy weighing 30 Kg. who received 1 Gm. of streptomycin per day for the treatment of tuberculosis of the lungs and lumbar spine. The throat cultures shown in the photographs were made daily on streptomycin agar from the beginning of therapy. The micro-organisms isolated from his cultures on streptomycin blood agar plates were *Micrococcus tetragenus* and a few yeasts. Patient BK was a twenty year old woman who was admitted for excision of a pilonidal cyst. She was given 2 Gm. of streptomycin per day and 300,000 units of penicillin procaine and 5 or 6 Gm. of sulfadiazine per day.

Figure 2 shows the results of cultures

seven patients in the Billings series because they had been receiving streptomycin for some time before the cultures were taken. It should be noted that all of the patients in this series received 1 Gm. or more of streptomycin per day. The results of cultures on these sixty-one patients can be seen in Figure 3.

The bacteria recovered from cultures on streptomycin media were for the most part representative of the ordinary flora of the normal human throat, i.e., staphylococci, green-forming streptococci, pneumococci, *Micrococcus tetragenus*, *Neisseriae* and some of the coliform group. The only unusual finding was a much higher incidence of yeasts or yeast-like fungi than is ordinarily encountered. These were not identified taxonomically. Colonies on blood agar and Sabouraud's medium resembled ordinary *Staphylococcus albus*. Most of

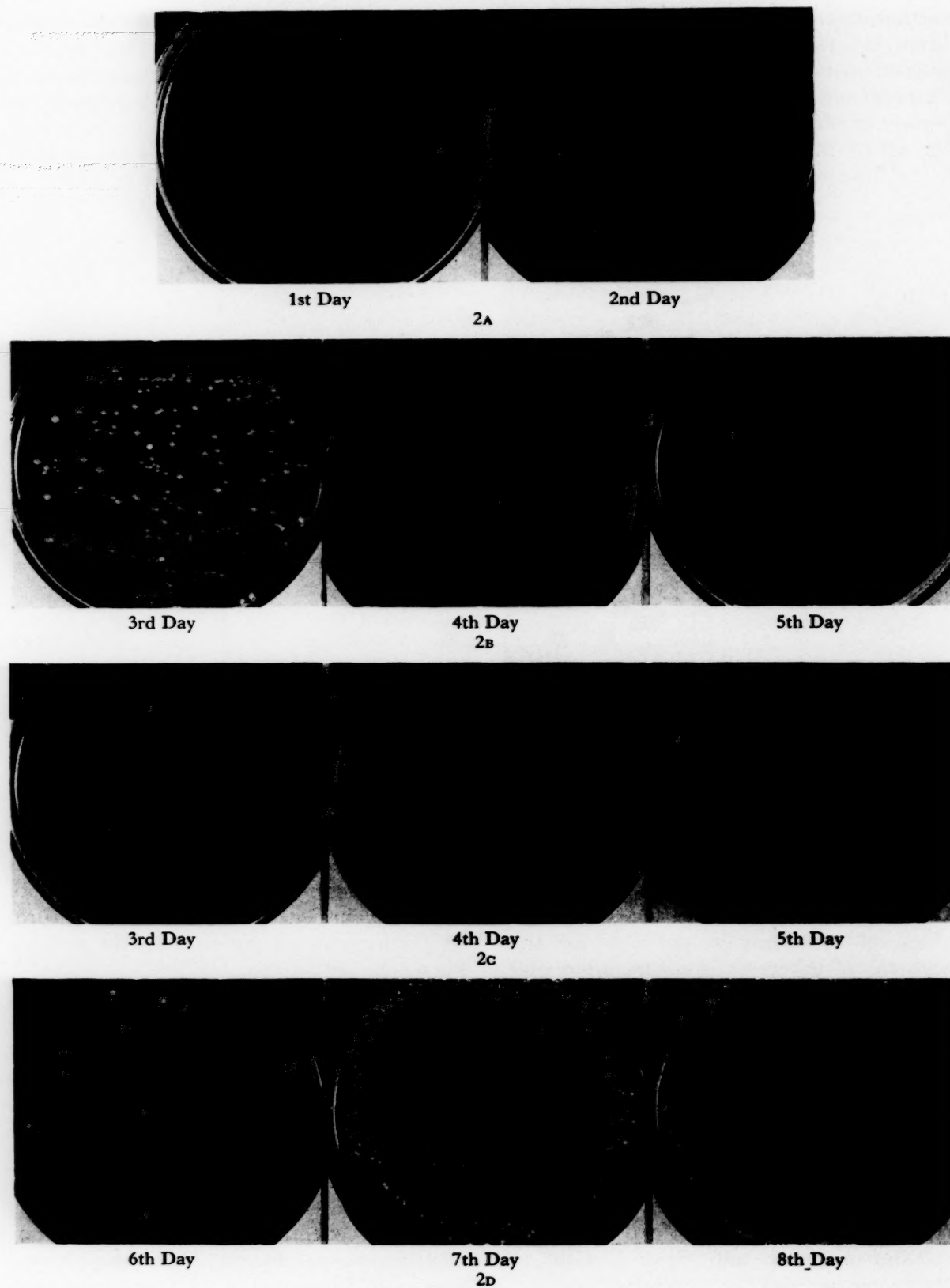


FIG. 2. Serial throat cultures in two patients receiving streptomycin. Numbers designate days of streptomycin therapy. A and B, patient P. G., C and D, patient B. K.

them produced no hyphae. Microscopically, the cells had the typical appearance of yeasts, large budding forms.

From the broth dilution cultures made to determine what proportion of the total bacterial population was streptomycin-re-

seven cultures containing some colonies of streptomycin-resistant organisms. (Fig. 3.) Three of these positive cultures consisted entirely of yeasts. Of the 157 members of the staff, student body, laboratory and clerical personnel, many of whom were cultured

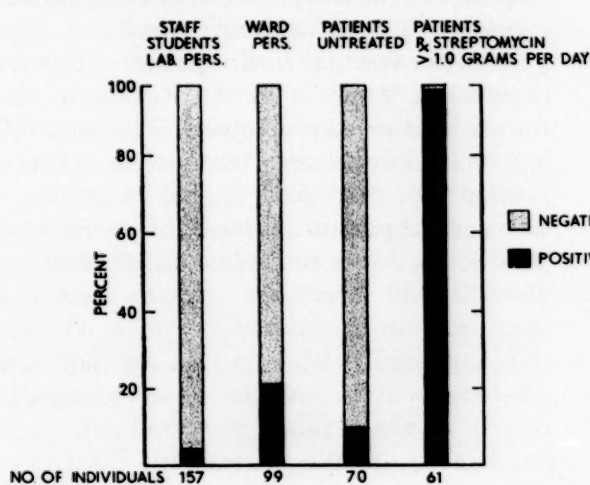


FIG. 3.

Figs. 3 and 4. Results of throat cultures on streptomycin media (200 µgm. per ml.).

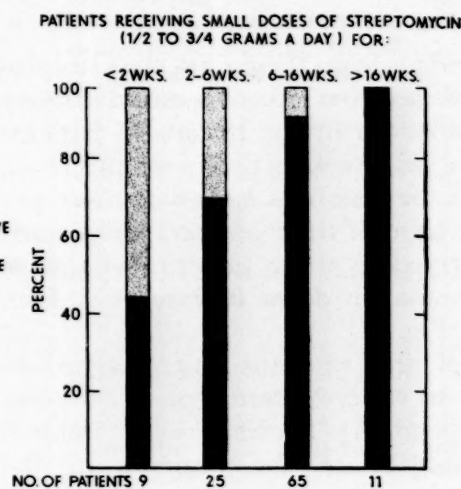


FIG. 4.

sistant or dependent it was found that ten to twenty times as many micro-organisms grew on the control media as on media containing 200 micrograms of streptomycin per cc.; in other words, 10 to 20 per cent of the micro-organisms swabbed from the throat were streptomycin-resistant or dependent. The concomitant administration of penicillin and/or a sulfonamide did not seem to retard the appearance of streptomycin-resistant or streptomycin-dependent organisms in the throat although it did reduce the variety of bacteria by eliminating most of the penicillin-sensitive and/or sulfonamide-sensitive organisms.

M.T.S. Series. A single culture was made on each of the patients in the second series who were receiving only 0.5 to 0.75 micrograms of streptomycin per day. The results of these cultures can be seen in Figure 4. It will be seen that a much smaller proportion of the cultures were positive during the first two weeks of therapy but that this proportion increased as treatment continued.

Among the seventy patients who were not receiving streptomycin there were

repeatedly, only six individuals had positive cultures, an incidence of 4 per cent. (Fig. 3.) Only one of these six patients had more than a few colonies per plate.

Among the ninety-nine members of the ward personnel, i.e., nurses and attendants, there were twenty-one positive cultures, an incidence of 21 per cent. (Fig. 3.) Four of these cultures showed heavy growth of streptomycin-resistant bacteria. It is interesting to note that these four cultures were from nurses who were at the time caring for patients receiving streptomycin.

Incidence of Streptomycin-dependent Bacteria. At least one culture on each of the patients in the Billings series was examined for streptomycin-dependent (type B) bacteria by picking eight or more colonies and subculturing onto streptomycin media (100 micrograms per cc.) and onto streptomycin-free media. Streptomycin-dependent bacteria were recovered in two-fifths of these patients as early as two days after treatment was started. The species encountered were green-forming streptococci, staphylococci, diphtheroids, gram-negative rods, *Neisseria catarrhalis* and *N. flava*. The twenty-one

positive cultures from nurses and ward attendants were similarly examined and streptomycin-dependent staphylococci were recovered from three, all of which were from nurses caring for patients receiving streptomycin.

COMMENT

It is evident from these data that streptomycin-resistant bacteria appeared among the normal flora in the throats of patients during the first week or two of streptomycin therapy if the dose was 1 Gm. or more per day. The time of their appearance seemed to be delayed in those patients who were receiving smaller doses (0.5 to 0.75 Gm. per day). Fig. 4.

Most of the resistant micro-organisms belonged to type A, but type B (streptomycin-dependent) bacteria were isolated from two-fifths of the patients in the Billings series. There is no reason to doubt that a more exhaustive study would have revealed the presence of greater numbers of dependent bacteria.

The micro-organisms recovered were all members of the species usually found in the normal human throat except that a greater number of yeasts was cultured than is ordinarily the case. In fact, a large proportion of the positive cultures in the control groups consisted only of yeasts or yeast-like fungi. These yeast-like micro-organisms were not identified. Most of them were presumed to be *Monilia* (*Candida* according to the newer terminology) because this is the yeast most commonly found in the human mouth.^{9,10} The high incidence in throat cultures on streptomycin media is a subject for further investigation.

It is of interest that penicillin and/or one of the sulfonamide drugs failed to prevent or even to delay the appearance of streptomycin-resistant organisms in the throat. Their administration did, however, eliminate the species most sensitive to those drugs. The change in flora was not as great as that described by Lipman, Coss and Boots¹¹ whose patients received much larger doses of penicillin for longer periods of time.

The highest incidence of streptomycin-resistant bacteria in untreated individuals occurred among nurses who were caring for patients undergoing treatment with streptomycin. This finding suggests that contact with these patients may have been responsible for the presence of streptomycin-resistant bacteria in their throats.

The unexpected finding of streptomycin-dependent bacteria in the throats of three nurses is as yet unexplained. The possibility has been considered that some substance present in the pharyngeal secretion of saliva of these individuals or a metabolic product of some microbial inhabitant may provide the necessary growth factor for streptomycin-dependent bacteria. We have thus far been unable to find any substance related to streptomycin or its derivatives which would replace streptomycin in the cultivation of the dependent bacteria *in vitro*.

SUMMARY

Specimens from the throats of patients receiving streptomycin were cultured onto streptomycin media in order to detect the presence of streptomycin-resistant and streptomycin-dependent bacteria. Streptomycin-resistant bacteria in large numbers were cultured from the throats of 98.4 per cent of sixty-one patients who were receiving 1 to 4 Gm. of streptomycin per day. They began to appear during the first thirteen days of treatment in the twenty-four patients who were followed from the beginning of streptomycin therapy.

Results of a single survey of another series of patients receiving small doses of streptomycin (0.5 to 0.75 Gm. per day) suggested that resistant flora appeared more slowly. These streptomycin-resistant bacteria all belonged to species normally inhabiting the human throat. Yeast-like forms (*Monilia*) were found in unusually high incidence. Streptomycin-dependent bacteria were found in two-fifths of the patients receiving large doses of streptomycin, i.e., 1 Gm. or more per day.

Streptomycin-resistant bacteria in small

numbers were recovered from only 4 per cent of 157 members of the hospital staff, student body and clerical personnel and from 10 per cent of untreated patients. The highest incidence of positive cultures in the control series, 21 per cent, occurred in the nursing and ward personnel. Strongly positive cultures were found in four nurses who were caring for patients receiving streptomycin.

Streptomycin-dependent micro-organisms were recovered from the pharynx and large bowel of mice and rabbits after one week of treatment with large doses of streptomycin.

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Immunization of Human Beings with Group A Hemolytic Streptococci*

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THE prevention of hemolytic streptococcal respiratory disease is among the most pressing problems confronting the student of infectious disease. Much disability results from acute suppurative illnesses caused by these organisms and the non-suppurative complications that so frequently follow.^{1,2} Ordinary public health methods have failed to control the spread of respiratory infection. The recent development of technics for the sterilization of air and the control of extrahuman reservoirs of infection³ have been of interest but have not been proved to be of value in the suppression of streptococcal disease and are not yet applicable to the population at large.

Sulfonamide chemoprophylaxis of hemolytic streptococcal infection was tested extensively in groups of rheumatic children and in the armed forces,^{4,5} and was successful until epidemics were established in which the causative agents were sulfonamide resistant strains of streptococci.⁶ Under no circumstances could this form of prophylaxis have been widely applied in population groups not under the immediate supervision of physicians because of the hazard of serious toxicity.

Because none of these measures directed toward the prevention of infection of human beings by hemolytic streptococci has been successful, it becomes essential that the usefulness of other measures be explored. The production of active antibacterial immunity by the parenteral administration of a streptococcal vaccine is one of these.

Gabritschewsky, who recognized the streptococcal causation of scarlet fever two decades before other investigators, prepared a vaccine from streptococci isolated from human beings suffering from this disease. This material was administered by him and other European workers to thousands of children in clinical experiments and appears to have been efficacious in reducing the frequency of occurrence of scarlet fever in the immunized groups.⁷ The method of preparation of the material, reactions which followed its use and results of serial Dick testing indicate that the vaccine contained not only streptococci but also large amounts of the erythrogenic substance of Dick. It is almost certain that the administration of this material reduced the incidence of scarlet fever by inducing the formation of antierythrogenic antibody similar to that produced by the injection of Dick toxin. Antibacterial immunity capable of reducing the frequency of hemolytic streptococcus respiratory disease without rash was probably not established.

Since 1924⁸ nearly all investigations of the problem of immunization in streptococcal disease have been directed toward the production of resistance to Dick toxin although it is now well known that these technics do not reduce the total incidence of streptococcal infection.⁹

Bloomfield and Felty¹⁰ used a polyvalent hemolytic streptococcus vaccine for the immunization of a group of nurses and obtained results suggesting that resistance to

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infection by these organisms had been increased. Reactions to the injections were mild.

The intravenous injection of hemolytic streptococci was undertaken some years later by other investigators for the purpose of decreasing the supposed hypersensitivity of rheumatic subjects to the organism, thus alleviating the acute illness and preventing recrudescence.^{11,12,13} In one study the results suggest that recurrences were less frequent and severe in the immunized subjects.¹¹ Whether this was the result of diminished sensitivity or increased resistance to infection of the respiratory passages by hemolytic streptococci cannot be ascertained. The report states that the frequency of respiratory disease in the treated and control groups was similar but the nature of the infectious processes which occurred has not been described. Reactions to administration of the vaccine intravenously were severe in the presence of active rheumatic fever and mild or absent in inactive cases.

Investigation of the structure of the hemolytic streptococci¹⁴ has demonstrated that the organisms pathogenic for man are members of a single serologic group (A) and that the members of this group may be further subdivided into types on the basis of two protein constituents of the bacterial cell, the "T" and "M" substances. Evidence has accumulated, obtained by protection tests in rodents, which indicates that resistance to infection by these streptococci is type specific and closely related to the M-anti-M antibody system.^{15,16} Confirmation of this point of view has been obtained by study of human disease and experimental streptococcal infection in monkeys.¹⁷

Evans in a series of papers^{18,19,20} has objected to the concept of type specific immunity and has presented experimental evidence which suggests strongly that certain strains of group A streptococci have a broad immunologic base and are able to stimulate antibodies capable of conferring protection in mice against streptococci of certain other types. Dubos²¹ has also pointed

out the paucity of information which is available in regard to group rather than type specific resistance to infection by streptococci and pneumococci.

This information indicates the importance of further investigation into the protective value of group specific immunity in streptococcal disease. Type specific resistance to infection is more potent and more easily evaluated epidemiologically and in the laboratory. It is, therefore, appropriate to begin an exploration of the usefulness of antistreptococcal immunization in human beings by studying in man the production of type specific antibodies and resistance to infection.

Two naval epidemiologic units have recently reported experiences in the use of group A hemolytic streptococcus vaccines for the control of respiratory disease in training stations in which epidemics caused by sulfonamide resistant streptococci of a very few types were in progress.²² Heat and ultraviolet-killed organisms were injected three times within a week. Reactions were mild with type 19 vaccine but severe and common when type 17 cells were added. No protection against natural infection by streptococci of the homologous types as the result of immunization was demonstrated in several experiments.

Another approach was adopted in this clinic since it seemed desirable to measure the production of type and group specific antibodies and to study the nature and severity of reactions that would be associated with the immunization of human beings with group A hemolytic streptococci before beginning work in the field.

MATERIALS AND METHODS

Preparation of Vaccine. The organisms used were group A hemolytic streptococci of types 3 and 17 isolated from the throats of infected human beings. They were in the matt phase when used and formed large amounts of acid soluble type specific material.¹⁴ Four liters of a broth culture of each, incubated for eighteen hours, were centrifuged and the sedimentary cells washed once with a large volume of sterile normal salt solution. The cells were again re-

covered by centrifugation, resuspended in 50 ml. of normal salt solution, killed by heat at 60 to 65°C. for sixty minutes in a water bath and preserved with .01 per cent formalin. The material was shaken for three hours in a Kahn shaker to reduce the granularity.

The suspension of type 3 contained 2.2 mg. of bacterial N per ml., that of type 17 contained 4.4 mg. per ml. Bacterial counts were not made of either preparation. Other experience indicates that 1 mg. of streptococcal N is equivalent to approximately 1 billion chains as determined by plate count.

Appropriate serial dilutions were made in sterile normal saline in such a way that the amount of vaccine to be administered was contained in from .1 to .5 ml. All injections were given subcutaneously in the deltoid region.

Antibody Determinations. *Anti-M antibody:* The technic of Rothbard²³ for the detection of anti-M type specific antibody was followed exactly. The single modification was the use throughout of the blood of one adult which permitted excellent growth of the test strains.

Anti-X antibody: An investigation has been conducted and reported in detail elsewhere²⁴ of a non-type specific, precipitating antigen which is present in acid extracts of matt group A streptococcal cells. It is not the "C" carbohydrate. Full details of the method of its preparation, the microprecipitin technic used for detection of its antibody, the antibody response which occurred following hemolytic streptococcal infection and the relationship of this antigen-antibody system to the clinical manifestations of hemolytic streptococcal disease have been presented.

Anti-C antibody: Purified group carbohydrate "C" was used as an antigen for the detection of anti-C precipitating antibody by means of a microtechnic described elsewhere.²⁴

Antistreptolysin: Antistreptolysin titers of the collected sera were measured by a method previously described.²⁵

Study Groups. *Group 1:* Group 1 was composed of ten males and one female, all of whom suffered from serious, disabling disease of the joints or nervous system. All but two were bed- or chair-fast.

Group 2: Group 2 was composed of thirty-two healthy male convicts whose mean age was 30.5 years with a range from eighteen to fifty-six years.

Antibody Response. *Group 1:* Six members of

Group 1 received type 3 and five received type 17 vaccine. An initial test dose of approximately 3 micrograms of N* was administered followed by eight subsequent injections at weekly intervals. Each case was titrated individually, the amount of vaccine being increased irregularly

TABLE I
TYPE SPECIFIC ANTIBODY RESPONSE IN GROUP 1

Total Vaccine Micrograms of N	Type 3		Type 17		Total Cases	
	No. of Subjects	No. with Antibody Response	No. of Subjects	No. with Antibody Response	No. of Subjects	No. with Antibody Response
80 to 90	3	1	1	0	4	1
160 to 190	1	0	2	0	3	0
370 to 520	1	1	1	1	2	2
2,600 to 3,700	1	1	1	1	2	2

TABLE II
X ANTIBODY RESPONSE IN GROUP 1

Total Vaccine Micrograms of N	Type 3		Type 17		Total Cases	
	No. of Subjects	No. with Antibody Response	No. of Subjects	No. with Antibody Response	No. of Subjects	No. with Antibody Response
80 to 90	1	0	0	0	1	0
160 to 190	1	0	1	0	2	0
370 to 520	1	1	1	1	2	2
2,600 to 3,700	1	1	1	1	2	2

Antibody present in 4 initially.

each week on the basis of the severity of reaction to the previous dose. Sera were collected aseptically from each subject before the immunizations were begun and again ten weeks later or one week after the last injection of vaccine.

Seven subjects accepted less than 190 micrograms of N and type specific antibody developed in only one. It was possible to administer from 370 to 3,700 micrograms of N to four subjects, in all of whom a type specific antibody response occurred. (Table I.)

Anti-X antibody developed during immunization in four of the seven subjects in whom it was not present in the initial serum. All of the responses were observed in persons who had received more than 370 micrograms of N. (Table II.) Anti-C antibodies failed to appear as the

* Here and subsequently this indicates that vaccine equivalent to this amount of N was injected.

result of immunization and no significant alteration of the antistreptolysin titer occurred.

Vaccine of both types 3 and 17 was equally capable of stimulating the production of these two antibodies and the quantitative relationships with each were similar.

TABLE III
DOSAGE SCHEDULE IN GROUP 2

No. of Injections of Vaccine at Intervals of 7 Days*	Total Dose of Vaccine in Micrograms of N	Number of Subjects
3	6 to 16	11
3	88 to 124	5
4	8 to 16	3
4	92 to 164	3
5	12 to 20	6
5	144 to 204	4

* Test and subsequent larger dose forty-eight hours later considered as single injection.

Group 2: All of the members of Group 2 received a test dose of 4 micrograms of N. Another injection of 40 micrograms of N was given forty-eight hours later to those who had not reacted strongly to the initial dose. Subsequent injections of vaccine were at seven-day intervals. The amount administered and the duration of the immunization were dictated by the severity of reactions. The number of men who received various courses and quantities of vaccine are summarized in Table III. Sera were collected before the immunization was begun and 8 weeks later. Neither a type specific, anti-X nor anti-C antibody response occurred nor did the antistreptolysin titer vary significantly in any subject.

Toxic Reaction to Immunization. Group 1: It quickly became apparent during the early phase of the immunization of Group 1 that there were very great individual differences in the tolerance of human beings for subcutaneously injected killed streptococci. These persons were so situated that they could not be kept under close observation and the degree of severity of reaction was necessarily determined by questions asked at the time of the subsequent injection. The data obtained are, therefore, not precise, but it is notable that by the fifth week two individuals were comfortably receiving doses of 400 micrograms of N, whereas four were accepting only 8 micrograms of N or less. The same situation prevailed at the end of the

immunization period except that the differences were greater. Two subjects then reacted strongly to the injection of more than 6 micrograms of N and two received 600 to 800 micrograms of N without difficulty.

The toxic phenomena were of three sorts: (1) systemic reactions with chills, malaise and aching; (2) swelling and soreness of the injected arm and (3) nodule formation. The latter complication was of interest. Certain subjects developed firm nodules at the site of injection that persisted for several weeks. They were tender initially but later became painless. Liquefaction of the nodule occurred on two occasions in one individual. The aspirated material from each was sterile. There was no difference in severity of reactions caused by vaccine prepared from the two types of streptococci.

Further description of the reactions to immunization in Group 1 is not feasible because clinical observations were inadequate.

Group 2: The subjects in Group 2 received an initial test dose of type 17 vaccine equivalent to 4 micrograms of N. Local reactions, characterized by erythema, soreness of the arm and occasionally persistent nodule formation in varying combinations occurred in twenty and were graded as severe in six. One of the latter suffered a generalized systemic disturbance as well. Twelve subjects who accepted the test dose without reaction received a ten-fold increment of vaccine (40 micrograms of N) two days after the first injection. Reactions to this amount were minimal or absent in all.

The quantity of vaccine administered each following week was based on the reaction to the test and subsequent injections of the material. None of the six subjects in whom severe reactions occurred initially was able to tolerate more than 2 micrograms of N, and one was ill and required rest in bed after an injection of only 1 microgram of N. Twelve of the fourteen subjects who suffered only a moderate initial reaction were able to accept 2 to 4 micrograms of vaccine as N throughout the planned course. Increasing sensitivity appeared in two. Five of the twelve subjects who did not react to the administration of 40 micrograms of N were able to continue at this level for four to five weeks. The remaining seven developed increased sensitivity to the injection of streptococci.

The development of accentuated reactivity in certain subjects to quantities of vaccine previously accepted without difficulty was notable.

The details of this phenomenon as observed in nine persons are presented diagrammatically in Figure 1.

The administration of 4 micrograms of N to subjects 4 and 18 was not associated initially with marked toxicity. One week later a similar quantity of vaccine invoked a moderately severe

local and general systemic reaction in one and a mild local disturbance in the other. On the following week the dose of vaccine was halved but moderately severe local and generalized reaction occurred in Subject 4 and similar but much more violent response in Subject 18.

A more dramatic sequence of events occurred

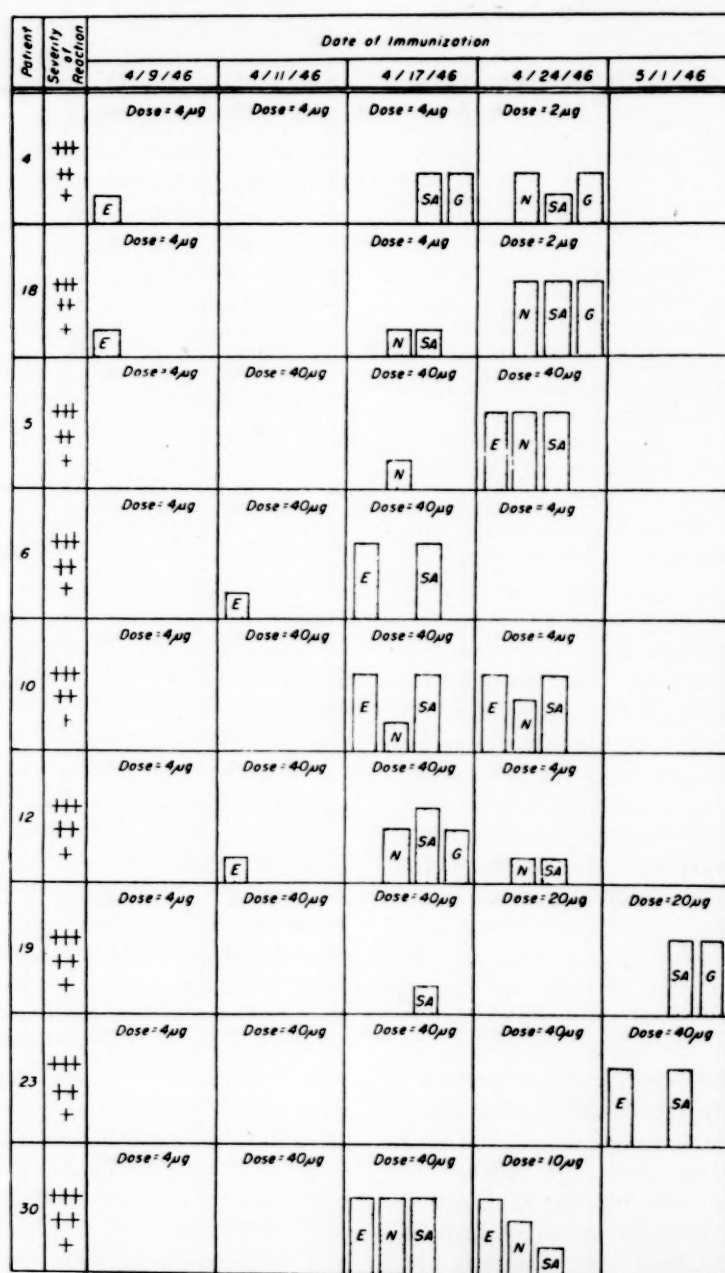


FIG. 1. Increasing reactivity to injection of group A hemolytic streptococci in nine subjects. The dose of injected vaccine is expressed as its equivalent in micrograms of N. Reactions: E, erythema; N, persistent nodule; SA, soreness of arm; G, generalized systemic disturbance. The height of the cross hatched column indicates the severity of the reaction.

in seven subjects who accepted an initial injection (forty-eight hours after the test dose) of 40 micrograms of N without difficulty. Severe local and in two marked generalized systemic reactions followed the second injection of 40 micrograms of N in four, the third in one and the fourth in two subjects. The toxic phenomena in these men consisted of extensive erythema of the skin around and the development of large persistent nodules at the site of injection in association with great local soreness and tenderness of the arm. Generalized systemic reactions with chills and malaise were also observed.

The course of immunization in Subject 10 was particularly interesting since the original injection of 40 micrograms of N caused no toxicity whatever. Two weeks later after his sensitivity to the streptococcus had increased a violent reaction followed the administration of only 4 micrograms of N.

The degree of the initial and the development of subsequent reactivity to the injection of streptococcal vaccine were correlated with the antistreptolysin titer and anti-X precipitin content of the pre-immunization sera obtained from each subject. The mean antistreptolysin titer of the sera of twenty men who responded to the test dose with a severe or moderately severe reaction was 84 units, that in the twelve non-reactors was 43 units.

Five of eleven subjects, or 45.5 per cent, whose initial serum contained anti-X antibody developed an increasing sensitivity to injection of streptococci; only four of twenty-one, or 19.0 per cent, in whom this antibody was absent did so. This is a significant difference but the observation is probably not entirely valid since a smaller number of subjects in whom this antibody was absent tolerated the large amount of vaccine which was most frequently followed by an enhanced reactivity.

COMMENT

An exploratory study of the immunization of human beings with group A hemolytic streptococci has been described. This work was undertaken primarily for the purpose of determining the total quantity of vaccine and duration of immunization that would be required for the production of type specific antibacterial antibodies. These immune substances, as detected by the Rothbard technic, and the non-type

specific anti-X antibody appeared in the serum of only those experimental subjects who accepted 370 micrograms of N or more in nine injections at weekly intervals. Shorter courses and smaller amounts of vaccine failed to induce an antibody response.

The data presented herein suggest that antistreptococcal prophylactic immunization will not be practical or useful if a demonstrable type specific antibody response is essential for its success. Few persons will tolerate the large amount of vaccine that must be administered over a long period of time in order to stimulate the production of these immune substances.

It is quite probable that resistance to infection by hemolytic streptococci can be enhanced by immunization although the procedure does not induce a measurable type specific antibody response. Success or failure of antistreptococcal technics under these circumstances can be studied only when epidemic conditions permit the evaluation of prophylactic methods in the field. This situation, which may well be that existing in man, is cumbersome and greatly limits the possible lines of attack on the problem of prevention of hemolytic streptococcal disease. If an antibody response had occurred regularly, it could have been used as a guide during the study of various prophylactic technics, as has been the case in the investigation of immunization against infection by *S. typhii* and the viruses of influenza A and B.

Toxicity as the result of injection of small numbers of heat killed group A hemolytic streptococci was severe. The reactions which occurred were principally local and consisted of erythema around and persistent nodule formation at the site of injection. It is impossible to determine whether the erythema was the result of reactivity on the part of the subjects to the Dick erythrogenic material which may not have been entirely removed from the streptococcal cells at the time of preparation of the vaccine since none of the experimental subjects was Dick tested.

The formation of persistent large nodules, initially tender but later becoming painless, at the site of injection of the vaccine was of great interest. Their nature cannot be ascertained in the absence of histologic examination. In certain instances generalized systemic disturbances with chills, malaise and aching of the joints were also observed.

The subjects of Group 2, following injection of a small number (circa 4 million cells) of killed group A streptococci, were divisible into two sharply defined groups: those who reacted vigorously to the test dose and those who accepted this and a ten-fold greater amount of vaccine without reaction. The basis for this sharp difference in reactivity cannot be elucidated. It seems wiser to regard the observed toxicity as a reaction to the erythrogenic substance especially since erythema was the principal manifestation of the disorders, until additional experiments have been conducted using a vaccine prepared from repeatedly washed streptococci and tested in subjects whose Dick skin reaction has been determined. The definite possibility exists that the manifestations of toxicity in these men were the result of sensitivity to some other fraction or product of the hemolytic streptococcus.

This position is strengthened by the fact that the mean antistreptolysin titer was higher in individuals who reacted strongly to the test dose than in those who did not, indicating that the former group had been more recently infected by hemolytic streptococci than the latter. This circumstance may have led to a state of more active streptococcal hypersensitivity in these men.

The increasing reactivity to the injection of hemolytic streptococci which was exhibited by certain subjects was of even greater interest than the initial toxicity of these organisms for others. This phenomenon occurred most frequently in those individuals who initially tolerated the administration of a large amount of vaccine without difficulty. Individuals who had received vaccine equivalent to 20 to 40

micrograms of N on one, two, or three occasions without reactions subsequently developed violent disturbances in response to similar or smaller amounts of the immunizing agent. Erythema and generalized systemic reactions were prominent features of these disorders but the formation of persistent nodules was more frequent in these subjects than in those in whom a high initial toxicity to streptococci was observed.

Only one interpretation of these results seems appropriate. The sequence of events in these individuals must be regarded as the result of the development of artificially induced hypersensitivity, presumably of an immunologic nature, to group A streptococci. It is not possible to suggest which antigenic fraction or product of the organism was responsible for the production of the altered tissue reaction.

An earlier analysis indicated that the presence of anti-X antibody in the pre-immunization serum was associated with a higher incidence of developing sensitivity. A more critical examination of the data reveals that subjects in whose sera this substance was initially present more frequently accepted the larger amounts of vaccine that were usually required for the stimulation of an increased reactivity.

The results of this study in human beings are consistent with those obtained in other animals^{26,27} which demonstrated that hemolytic and non-hemolytic streptococci are remarkably effective sensitizing agents when injected locally. Elsewhere²⁸ it was predicted that hypersensitivity might develop if antistreptococcal immunization were undertaken in man and that this might lead to a greater susceptibility to rheumatic fever and other non-suppurative complications of hemolytic streptococcal disease if prophylaxis against infection by hemolytic streptococci was incomplete. This remains a grave possibility.

Theoretic considerations have suggested that the production of active immunity to infection by group A hemolytic streptococci should be most difficult since resistance to infection may be type specific. If this is the

case, a polyvalent vaccine containing cells of all the types of streptococci causing disease in the community would be essential. The information obtained in this study suggests that large numbers of organisms of each type would probably be required in the immunizing preparation and that adequate amounts of the mixture could be administered to few human beings because of its probably high initial toxicity. Added to these difficulties would be the great hazard of sensitization of the immunized persons.

Future investigation of prophylactic immunization against hemolytic streptococcal infection should include experimental study of non-type specific immunity. In addition, chemical methods should be utilized for the purpose of separating the immunizing from the sensitizing and toxic fractions or products of the streptococcus. The route of administration of the immunizing substance should also be evaluated since intravenous injection of the antigen may be less likely to induce sensitization.²⁹ Work along these lines might lead to the development of technics suitable for the control of monotype epidemics in large semi-closed groups, such as those present in schools and the armed forces, even if not applicable to the population at large.

SUMMARY

1. Heat-killed group A hemolytic streptococci were administered subcutaneously to human beings.

2. Type specific and other antibacterial antibodies developed only in those subjects who received a very large amount of vaccine over a nine-week period.

3. Toxic reactions were severe following the injection of small amounts of vaccine in certain persons. Others accepted much larger amounts without difficulty.

4. Increased reactivity to the injection of hemolytic streptococci developed in some subjects. This is believed to represent artificially induced sensitivity of an immunologic type to the streptococcus or its products.

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Treatment of Acute Rheumatic Fever with Aspirin*

With Special Reference to the Biochemical Changes

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SALICYLATES have remained the drug of choice in the treatment of acute rheumatic fever ever since MacLagen¹ introduced the use of salicin in this disease. It is a commonly recognized fact that adequate doses of salicylates produce a prompt remission of fever and swelling in the joints and prevent extension of the disease process. It is believed by Coburn² and others that prompt suppression of the rheumatic inflammation may prevent development of cardiac manifestations of the disease. Murphy³ however, could find no anatomic evidence of the ameliorating effect of salicylates.

The most common method of administering salicylates has been in the form of sodium salicylate. Large doses have been prescribed for over forty years. Lees⁴ in 1903 recommended doses of 150 to 200 gr. (10 to 13.3 Gm.) daily. Coburn,⁵ utilizing an accurate method for the determination of plasma salicylate, laid down criteria for adequate treatment. He believed that the dose should be high and frequent enough to produce and maintain a plasma salicylate level of 36 mg. per 100 cc. (360 micrograms per cc.) and thought that this could be best accomplished by intravenous injection. The gastric irritation frequently accompanying peroral administration of sodium salicylate has led to the prescription of sodium bicarbonate along with sodium salicylate. This modification became all the more popular because symptoms of salicylism

were less likely to occur with its use. It is now recognized, however, that salicylism is avoided when bicarbonate is used because the plasma salicylate levels are lowered.

Because of the gastric irritation frequently encountered with sodium salicylate medication, many clinicians have tended to use aspirin in high doses in the treatment of acute rheumatic fever. However, there are few published reports of its use.⁶ Recently, during the course of the clinical evaluation of a new aspirin tablet containing aluminum hydroxide, an opportunity presented itself for study of the effect of aspirin in high doses on the course of acute rheumatic fever and of some of the biochemical changes that occur during its administration. This report deals particularly with the findings in respect to sedimentation rate, prothrombin concentration and acid-base balance.

METHODS

One hundred successive adult patients with acute rheumatic fever were treated with doses of aspirin estimated to produce and maintain plasma salicylate concentrations of 30 to 35 mg. per 100 cc. (300 to 350 micrograms per cc.). All these patients had the usual criteria of the disease: sudden onset of pain, swelling and tenderness in multiple joints with fever and rapid sedimentation rate. Some were seen in the first attack; many others had had previous episodes; a number had evidence of rheumatic carditis. In only eighty of these were extended chemical studies made, and these form the basis for this report.

* From the Hektoen Institute for Medical Research of the Cook County Hospital. This work was supported by a grant from The Wander Co., Chicago, Ill. and A. Wander, Ltd., London, England.

At weekly intervals venous blood samples were drawn under oil and the serum analyzed for the following constituents: sodium by the method of Hoffman and Osgood,⁷ chloride by the method of Schales and Schales,⁸ bicarbonate by the volumetric method of Van Slyke⁹ with

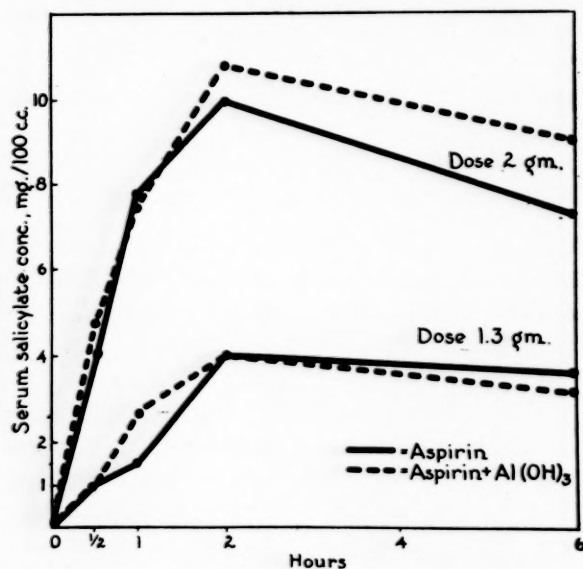


FIG. 1. Plasma salicylate concentrations after single doses of aspirin with and without aluminum hydroxide.

the assumption of a pH of 7.4, sedimentation rate corrected for anemia according to Wintrobe¹⁰ and prothrombin concentration by the Quick¹¹ method calculated as percentage of normal based on a normal control. Serum salicylate determinations were made by the method of Brodie, Udenfriend and Coburn⁵ by ethylene dichloride extraction. Urinary partitions of salicylate were estimated by the scheme of Smith and his co-workers.¹² In a number of patients blood pH determinations were made at the bedside with the aid of a Coleman pH meter calibrated at 38°C.

The aspirin used for this study was Alasil,* tablets containing 4 gr. of aspirin, 2 gr. of colloidal aluminum hydroxide and an excipient. Control tablets of aspirin were also used which were of the same size and which contained 4 gr. of aspirin but 2 gr. of starch instead of aluminum hydroxide. Preliminary tolerance curve experiments as illustrated in Figure 1 demonstrated that the plasma salicylate levels achieved after single doses of either form of aspirin were essentially the same. Of sixty-five patients given the control tablets in the high therapeutic doses eight (or 13 per cent) complained of local

gastric distress or heartburn. These symptoms were relieved when the tablets containing aluminum hydroxide were substituted for the control tablets without the knowledge of the patient. However, as will be seen later, many of these patients developed salicylism with either form of aspirin if the plasma salicylate level was high enough. It was not easy at this stage to distinguish between the distress due to local irritation and the nausea and vomiting of cerebral or systemic intoxication. Since the plasma salicylate levels and other chemical findings were indistinguishable when aspirin with or without aluminum hydroxide was used, the remainder of the paper will be made without reference to the presence or absence of aluminum hydroxide in the medicament although for most of the period of study of each patient he was receiving the aluminum hydroxide-aspirin combination.

RESULTS

Clinical Response to Aspirin. On dosages ranging from 4 to 6 tablets every four hours (96 to 144 gr. per day depending on the weight, or about 128 mg. per day per Kg. of body weight) the patients usually experienced relief of fever, pain and tenderness in the involved joints in twenty-four to forty-eight hours, even before the plasma salicylate concentration had risen to levels of 30 or more mg. per 100 cc. Such concentrations were usually achieved by the third day by this method of medication. Thus, the analgesic and antipyretic effect of the salicylate could be accomplished without high plasma salicylate concentrations. To produce these effects it was not necessary to employ intravenous injections or the hourly oral doses so popular in the past. Once the desired plasma level had been achieved it could be maintained by the same dose of 4 to 6 tablets given every six hours instead of every four hours. Complete subsidence of the swelling and mobility of the joints usually followed soon after the relief of pain. The patients were kept in the hospital until they were clinically well, but many had to be discharged before the sedimentation rate had returned to normal. The hospital stay ranged from fourteen to

* Supplied by the House of Wander.

eighty-seven days with an average of thirty-six days. Those who stayed for thirty or more days usually had findings of acute cardiac involvement, some with increased P-R intervals in the electrocardiogram and others with pericarditis. The response of these patients to salicylate therapy was slow but their symptoms finally subsided without any other medication.

Salicylism. Almost all patients in whom levels of 30 to 40 mg. per 100 cc. were maintained for several days developed one or more of the symptoms of salicylism. These included tinnitus, partial deafness, pounding in the head, nausea and vomiting and a general feeling of intoxication. As in alcoholic intoxication, mental disturbances were often manifested by excitability, negativism and irresponsibility, as recently described by Huntington *et al.*¹³ It was at this stage that many patients refused to cooperate in taking the medication. They used various subterfuges to avoid swallowing the tablets which they recognized as having a causal relation to their new symptoms. In this respect aspirin was no different from sodium salicylate. With either medication, if sufficiently high plasma salicylate concentrations were reached, symptoms of salicylism were likely to occur. Moreover, when sodium bicarbonate was given in addition to the aspirin, relief of symptoms occurred only because of the lowering of the salicylate levels. If higher doses of aspirin were then given and the plasma levels allowed to attain their previous high values, salicylism recurred in spite of bicarbonate medication.

In the uncooperative patient failure to take the medication continuously could often be ascertained only by a rapid drop in the plasma salicylate levels. The patient was often able to hide from the nurse the fact that he had not swallowed the tablets. The importance of frequent plasma salicylate determinations as a guide to effective rheumatic fever therapy is thus clearly indicated as is one of the chief advantages of the intravenous therapy recommended by Coburn. When the plasma salicylate level was found to be low, cooperation could

usually be effected by the use of smaller doses. Thus, the eighty patients in the study could be divided into two groups: forty-one patients in whom the average plasma salicylate level was maintained above 25 mg. per 100 cc. and thirty-nine in whom the

TABLE I
EFFECT OF ASPIRIN THERAPY ON SEDIMENTATION RATE

Total no. of patients with initially elevated sedimentation rate.....	80
i. No. of patients with average salicylate levels above 25 mg. per 100 cc.....	41
No. of patients with sedimentation rate normal at discharge.....	23
No. of patients with sedimentation rate still elevated at discharge.....	18
ii. No. of patients with average salicylate below 25 mg. per 100 cc.....	39
No. of patients with sedimentation rate normal at discharge.....	17
No. of patients with sedimentation rate still elevated at discharge.....	22

average level was below 25 mg. per 100 cc. This involuntary division was made the basis for a comparative evaluation of high or moderate salicylate doses.

Sedimentation Rate. The sedimentation rate of all the rheumatic fever patients was high at the time of admission. It usually ranged between 30 and 40 mm. per hour after correction for anemia. In a few instances the sedimentation rate fell rapidly but never so fast as the fever and swelling. In many patients the sedimentation rate was still elevated at the time of discharge from the hospital when all clinical symptoms had already disappeared. Comparison of the effect of high and low plasma salicylate concentrations on the sedimentation rate (Table I) showed only a slight superiority of the high levels in reducing the sedimentation rate to normal by the time clinical symptoms had completely disappeared. Seventeen of thirty-nine patients were able to achieve this result with moderate levels, as had been found by Manchester,¹⁴ while twenty-three of forty-one accomplished it on average levels higher than 25 mg. per 100 cc.

Prothrombin Levels. The concentration of prothrombin was expressed for convenience as inversely proportional to the prothrombin time rather than on the basis of a prothrombin curve. The error involved in this

assumption is not important for moderate reductions of prothrombin. Ever since Link¹⁵ showed that salicylate was a probable end product of the metabolism of dicumarol, a fear has been created that salicylate therapy can produce a hemor-

TABLE II
EFFECT OF ASPIRIN THERAPY ON PROTHROMBIN LEVEL

Total No. of Patients.....	66
I. No. of patients with average salicylate level above 25 mg. per 100 cc....	31
No. of patients with prothrombin below 75 per cent.....	10 (32%)
No. of patients with prothrombin above 75 per cent.....	21 (68%)
II. No. of patients with average salicylate levels below 25 mg. per 100 cc.....	35
No. of patients with prothrombin below 75 per cent.....	12 (34%)
No. of patients with prothrombin above 75 per cent.....	23 (66%)

rhagic tendency by lowering the prothrombin concentration. Several reports^{16,17} have intimated such an effect, especially in children. Weekly prothrombin time estimations were made in sixty-six of our patients. In general it was found that there was very little change in the prothrombin levels whether the patients were on high or on low doses of aspirin. In only 33 per cent of the patients was there a fall below 75 per cent of normal. Even in these instances the drop was usually moderate and the level tended to return to above 75 per cent of normal with continuation of the medication. No relationship could be found between the incidence of lowered prothrombin levels and plasma salicylate concentrations (Table II), the same percentage being found in the high and in the low plasma salicylate groups. In only one instance was there a fall of prothrombin to a dangerously low level. Here the concentration was calculated as 20 per cent of normal. The only clinical manifestation of hemorrhagic tendency which this patient manifested was a prolongation of the menstrual period. This bleeding was promptly stopped by the injection of two ampules of vitamin K (9.6 mg.). Thereafter the patient's prothrombin level remained in the normal range with continued aspirin therapy and

no further administration of vitamin K. At the time of the prolonged menses the plasma salicylate level was only 19.8 mg. per 100 cc. Thus, these data do not support the claim of Link and others that salicylate therapy has a specific effect upon prothrombin concentration. The isolated instances of a tendency toward bleeding can be more reasonably regarded as manifestations of idiosyncrasy.

Acid-base Balance. Serum chloride, sodium and bicarbonate determinations were made weekly during the course of salicylate therapy. Most patients experienced a moderate reduction of serum bicarbonate. If the lowest serum bicarbonate value found for each patient was chosen, twenty-four patients had values below 40 vols. per 100 cc. (18 mEq. per L.), forty-seven had levels between 40 and 50 vols. per 100 cc. (18 to 20 mEq. per L.) and nine had levels above 50 vols. per 100 cc. (Table III). The bicarbonate levels had no determining effect upon the incidence of salicylism, except in so far as low bicarbonate concentration was more likely to occur with high plasma salicylate. Salicylism occurred with both high and low bicarbonate. Its appearance seemed to be related only to the plasma salicylate concentration as previously mentioned.

Serum chloride concentration was found to be elevated in the majority of instances, the highest levels being found in the group with the lowest bicarbonate concentration. The range of chloride values found in each patient at the time of lowest serum bicarbonate was from 98.6 to 118 mEq. per L., the overall average being 108.6. In the group of low bicarbonate levels (below 40 vols. per 100 cc.) serum chloride averaged 110 mEq. per L. Serum sodium concentrations, on the other hand, were usually within normal limits but on the low side. The range was from 134 to 147 mEq. per L., the average being 140.3 for all the patients and only slightly lower (139.8) in the patients with serum bicarbonate below 40 vols. per 100 cc. These findings, which are summarized in Table III, are similar to

those found by Guest, Rapaport and Roscoe.¹⁸

Blood pH determinations were not made until near the end of the study. In fifteen patients in whom the pH determination was made at the bedside at the time of high

were then repeated. Urine pH determinations were made in both experiments. The details of these experiments will be reported elsewhere.

The clearance of salicylate and chloride before and after bicarbonate could not be

TABLE III
ACID-BASE FINDINGS DURING ASPIRIN THERAPY

	No. of Cases	Lowest Serum Bicarbonate mEq./L.		Serum Chloride mEq./L.		Serum Sodium mEq./L.		pH	
		Range	Average	Range	Average	Range	Average	Range	Average
Total	80	14-25	19	98.5-118.5	108.6	134-147	140.3		
	24	14-18	..	101-118.5	110.1	134-145	139.8		
	47	18-22	..	100-114.3	107.0	134-146	140.4		
	9	22-25	..	98.5-110.5	104.1	137-146	141.0		
Blood pH	15	7.30-7.51	7.41
Urine pH	30	4.88-6.60	5.42

plasma salicylate levels the values ranged between 7.30 and 7.51 with an arithmetical mean of 7.41. (Table III.) These values appeared to show little deviation on either the acid or basic side of normal in spite of the lowered serum bicarbonate.

Determinations were made of the pH of freshly passed urine specimens in thirty patients at the height of the aspirin therapy. The urine pH ranged from 4.88 to 6.30. However, there were only two values above 6.00. The arithmetical mean was 5.42.

Salicylate and Chloride Clearance. To determine whether there was any relation between chloride and salicylate excretion and what the effect on alkali was on these, a series of clearance studies were carried out on twelve patients during convalescence from acute rheumatic fever and while still in aspirin therapy. Plasma and urinary salicylate determinations were made by ethylene dichloride extraction in duplicate one-hour clearance tests. Chloride and creatinine clearances were likewise determined. After these tests the subjects were placed on an alkalinizing regimen, 2 to 3.3 Gm. of sodium bicarbonate every six hours for three days, in addition to the regular aspirin doses. The clearance tests

compared directly because the creatinine clearances were found to be lowered by the alkalinizing regimen. To rule out the effect of altered glomerular filtration the salicylate and chloride clearances were expressed as percentages of the simultaneously determined creatinine clearances. When the apparent salicylate clearance was determined on the basis of the ethylene dichloride extraction and expressed as the percentage of the creatinine clearance (called S/C), the values ranged from 1.36 to 5.78 for urines the pH of which ranged from 4.98 to 5.99. In the urine of pH of 6.60 the S/C was 9.51, and in that with pH of 6.68 the S/C was 11.7. After alkalinization the urinary pH ranged from 6.22 to 7.98. The S/C values rose in all cases, the lowest value of 6.62 being found with the urine of pH 6.22 and the highest of 33.3 for a urine of pH 6.98. In general the clearance was increased three to eight times by alkalinization. Chloride clearances, similarly expressed as percentages of the creatinine clearance, Cl/C, ranged from 6.5 to 3.16. On the alkaline regimen, chloride clearance was increased significantly in seven of twelve experiments as might have been expected;¹⁹ but in five experiments there

was either little change or slight depression of the chloride clearance.

During the course of these clearance experiments the work of Smith and his co-workers¹² on the fractionation of the urinary salicylate came to our attention.

salicylate was markedly increased, it became apparent that the principal effect of alkalization was on the excretion of free salicylate rather than on the conjugated derivatives. These findings are in general agreement with those of Smith and his

TABLE IV
SALICYLATE AND CHLORIDE CLEARANCES AND DISTRIBUTION OF URINARY SALICYLATE DURING ASPIRIN THERAPY WITH AND WITHOUT SODIUM BICARBONATE

Case	NaHCO ₃	Urine pH	Serum Chloride mEq./L.	Plasma Salicylate mg./100 cc.	Creatinine Clearance cc./min.	Cl/C*	Apparent† S/C	Apparent‡ SA/C	SA§ mg./100 cc.	SU§ mg./100 cc.	ST§ mg./100 cc.	SA/ST
1	None	5.99	104.7	29.5	94.3	1.73	3.13	1.95	12.8	13.9	60.6	0.21
	13.3 Gm. daily	7.14	93.5	6.0	63.9	5.66	23.5	17.2	13.5	9.8	39.1	0.35
4	None	5.70	100.2	29.0	91.2	0.98	4.28	2.68	15.7	21.1	88.9	0.18
	13.3 Gm. daily	7.55	105.0	16.1	86.4	1.23	26.8	22.9	116.8	19.3	189.2	0.62

* Cl/C = Chloride clearance ÷ creatinine clearance ratio.

† Apparent S/C = ratio of salicylate clearance to creatinine clearance when the salicylate clearance is calculated from plasma and urine salicylate concentration determined by ethylene dichloride extractions and no account is taken of the bound portion in the plasma.

‡ Apparent SA/C = same as S/C except that salicylate clearance is determined from free salicylate in urine (SA).

§ SA = free salicylate concentration in urine; SU = salicylurate concentration in urine; ST = total salicylate concentration in urine.

Smith's technic involved extraction of urine with both ethylene dichloride and carbon tetrachloride and calculation of the urinary salicylate in terms of free salicylate, salicylurate and total salicylate from empirically derived equations. Fractionations were made by this method in six of the twelve clearance experiments. If the salicylate clearances were estimated on the basis of the free salicylate excreted and again expressed as percentages of the creatinine clearances, the values found ranged from 0.84 to 2.43. However, during alkali administration these values rose to values two to eight times as high. Thus, there was no doubt that salicylate excretion for any given plasma salicylate level was markedly increased when more base was available for urinary excretion. Since on the alkaline regimen the ratio of free salicylate to total

co-workers. Representative data in two experiments are shown in Table iv.

COMMENTS

The clinical and laboratory findings in the eighty patients with rheumatic fever in whom intensive studies were made are in accord with the prevailing view that aspirin in large doses is a convenient and satisfactory form of salicylate medication. The local gastric irritation so often found with sodium salicylate occurred only occasionally in these patients and it was avoided completely when the tablets containing aluminum hydroxide were used. There were no recognizable untoward effects, locally or systemically, from the aluminum hydroxide. The ease with which the desired salicylate levels were achieved and maintained confirmed the findings with single doses that

salicylates are promptly absorbed from the intestinal tract. Since it has already been shown by Lester *et al.*,²⁰ and confirmed in unpublished studies by us, that the salicylate found in the blood after a dose of aspirin is almost entirely free salicylate, there is no contraindication to the use of aspirin on this score. In fact, Lester believes that the small quantities of acetylsalicylic acid found for a short time in the blood after a dose of aspirin have a greater analgesic effect than does free salicylate. Another advantage of the use of aspirin, with or without aluminum hydroxide, is that it is unnecessary to administer sodium bicarbonate. A still further advantage will be recognized later in the discussion.

The absence of serious increases in the prothrombin time in this group of patients is heartening for recent reports of the possible hemorrhagic danger of salicylate therapy have tended to discourage its use. Since at present the only effective remedy in acute rheumatic fever is salicylate in one form or another, it would be unfortunate if physicians were deprived of its use on inadequate grounds. The occasional patient who shows an unusual lowering of prothrombin concentration with a tendency toward bleeding can easily be treated with vitamin K. Whether aspirin (or aspirin with aluminum hydroxide) produces less alteration of the prothrombin time than sodium salicylate could not be determined, but it has been our general impression that in the many hundreds of patients treated with sodium salicylate in this hospital very little hemorrhagic tendency has been encountered.

The original plan of therapy in this study was to give doses of aspirin high enough to maintain the plasma levels recommended by Coburn. This procedure was found impossible by oral therapy in almost one-half of the subjects. In these patients a compromise was reached in which the patients were given doses that would keep the plasma levels just below salicylism. This dose was 12 to 20 gr. (0.8 to 1.3 Gm.) every four hours until the desired level had been reached and then the same dose every six

hours. In these patients maintained at plasma salicylate levels between 20 and 25 mg. per 100 cc. the therapeutic results were only slightly less satisfactory than those with higher doses. From a practical point of view, it may be safer to use moderate doses and have the assured cooperation of the patient than to insist on the high doses which require constant vigilance and frequent plasma salicylate determinations.

The significance of the lowered serum bicarbonate found during salicylate therapy remains controversial. Does salicylate ingestion produce a primary alkalosis due to respiratory stimulation with compensatory fall in bicarbonate or does it produce a primary fixed acid acidosis with compensatory respiratory stimulation? That toxic doses of salicylate, especially in children, produce marked hyperpnea is well recognized. In a recent case of aspirin poisoning in an eighteen month old child seen by us, we encountered a respiratory rate of more than 70 per minute, far greater than is seen in diabetic coma. Such respiratory stimulation with elevated serum pH has been reported by Coombs *et al.*²¹ and also by Ryder *et al.*²² who also found an alkaline urine. In experimental salicylate intoxication in dogs, Rapaport and Guest²³ as well as Boyle *et al.*²⁴ were able to demonstrate an initial rise in the serum pH followed by a fall in serum bicarbonate with a compensated return of the pH toward normal. Guest *et al.*,¹⁸ in a clinical study of children with rheumatic fever treated with sodium salicylate, presented further evidence that the primary effect was respiratory stimulation with alkalosis. They regarded both the lowering of bicarbonate and the retention of chloride as secondary compensatory phenomena.

On the other hand, Erganian *et al.*²⁵ found a lowered serum pH and thus acidosis in thirteen cases of salicylate intoxication in infants. Dodd²⁶ had similar findings. Our own data offer no support to the idea of primary alkalosis. The pH of the blood was usually about normal, and there were as many deviations to the acid side as to the

basic. Also, hyperpnea was not a noticeable feature of the symptomatology of our patients during any stage of therapy. Furthermore, alkaline urines were never encountered. For the most part, the urine specimens were highly acid even though ketone bodies were seldom seen in these adult patients. Like Rapaport and Guest we found a tendency toward elevated serum chloride concentrations with normal or slightly lower than normal serum sodium concentrations. Since the plasma salicylate at levels of 40 mg. per 100 cc. produced a displacement of only 3 mEq. of bicarbonate per L. and since no retention of other acids was seen, the lowered bicarbonate was evidently related to the elevated chloride and slightly lowered sodium. These findings associated with acid urine are consistent with those of a fixed acid acidosis.

It is possible to achieve a harmonious explanation of these apparently irreconcilable findings in a manner similar to that offered by Erganian *et al.*²⁵ A rapid rise in plasma salicylate concentration, especially like that seen in salicylate poisoning in children or in experimental salicylate infusion into animals, has as its primary pharmacodynamic action a stimulation of the respiratory center with rapid removal of free carbonic acid and production of an alkalosis of carbonic acid deficit. Compensation tends to take place by neutralization of base bicarbonate by the plasma proteins and particularly by hemoglobin. The ultimate compensation is by excretion of alkali in the urine. However, independent of this action of salicylate, is its own acidifying action and its effect in increasing the excretion of sodium and retention of chloride. These latter phenomena would produce an acidosis which would require for compensation a respiratory stimulation which has already been produced independently. Thus, the two actions of salicylate are mutually compensatory, and the net effect is a blood pH nearly normal in the presence of lowered bicarbonate and elevated chloride. An additional compensation may be the expansion of extracellular space

including plasma volume as recently reported by York and Fisher.²⁷ If the accumulation of salicylate is relatively slow, as in our patients, the primary hyperventilation may be slight and the acidosis effect more significant. Individual sensitivity of the respiratory center, too, may be a determining factor in production of the primary alkalosis.

Our clearance studies show that salicylate, like chloride, has a very low clearance. Even if, as Smith and Lester have pointed out, only about one-fourth of the plasma salicylate is in the unbound state when the concentration is about 30 mg. per 100 cc. (the remainder being bound to serum proteins), the clearance of salicylate is still very small compared with that of creatinine. Apparently most of the unconjugated salicylate filtered through the glomeruli is reabsorbed by the tubules unless an excess of base is available for simultaneous excretion with it. Under these circumstances it may be that both chloride and salicylate compete for the limited amount of base available for excretion, and when the urine is highly acid both chloride and salicylate are reabsorbed and retained. When extra alkali is furnished and the urine pH rises considerably, much larger quantities of salicylate can be excreted. In the majority of experiments it was possible to demonstrate that chloride under these circumstances was also better excreted. Thus, the acidosis effect of salicylate can be explained by the enforced retention of both salicylate and chloride.

If the acidifying effect of salicylate serves as compensation for the primary hyperpnea, it is apparent that aspirin which is administered as a free acid without sodium is preferable to sodium salicylate in producing this action. This may be why in our patients we could not corroborate the high blood pH values reported by Guest and Rapaport. Conversely, in aspirin or salicylate poisoning administration of sodium bicarbonate is mandatory in spite of any primary alkalosis for the only rapid way to lower the plasma salicylate concentration

is to alkalinize the urine. In the case of salicylate poisoning just mentioned, rapid amelioration of symptoms was produced by administration of glucose and sodium lactate intravenously and of sodium bicarbonate by stomach tube in what appeared to be a dying baby. This treatment is in accordance with that recommended by Barnett et al.²⁸ The fear expressed by Krasnoff and Bernstein²⁹ of using sodium bicarbonate by stomach tube because of the danger of increasing the absorption of whatever salicylate is still in the stomach is unfounded since the amount absorbed is small compared to the increased excretion due to the alkali.

SUMMARY

Eighty adult patients with acute rheumatic fever were treated with aspirin until disappearance of clinical symptoms of the disease. Of sixty-five patients started with control tablets of aspirin eight complained of gastric distress following ingestion. This distress disappeared when tablets containing aspirin and aluminum hydroxide were substituted. For most of the period of therapy in all patients, aspirin plus aluminum hydroxide was administered.

Some symptoms of salicylism occurred in almost all patients when the plasma salicylate level was more than 30 mg. per 100 cc. Only forty-one patients could be maintained at this level; thirty-nine had to be given doses that produced levels under 25 mg. per 100 cc. The sedimentation rate subsided to normal in a slightly larger proportion of patients in the group with high plasma salicylate levels.

The prothrombin concentration was only slightly affected by aspirin therapy. A drop below 75 per cent of normal occurred in one-third of the cases, there being no difference in incidence in the high or moderate dose groups.

A moderate fall in serum bicarbonate occurred in most cases, associated with an elevated serum chloride and a slightly diminished serum sodium. The blood pH was usually normal. The urine was usually

acid. It is believed that salicylate produces a primary hyperpnea with alkalosis but that the accumulated salicylate produces a fixed acid acidosis and that the two effects are mutually compensatory.

The apparent salicylate clearance after aspirin therapy is only about 3 per cent of the creatinine clearance when the urine is highly acid. It increases three to eight times when the urine is alkalinized with sodium bicarbonate. Most of this increase is in free salicylate. Alkalinization is therefore of prime importance in the treatment of salicylate poisoning.

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Relative Infectivity of Blood and Cerebrospinal Fluid in Secondary Syphilis*

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INVASION of the central nervous system of the human host by *Treponema pallidum* is related to the primary dissemination of the organism by the blood. In 1913 Uhlenhuth and Mulzer¹ showed that the blood of patients with primary or secondary syphilis was infectious in the rabbit. Of fifty-five cases of primary or secondary syphilis the blood of forty-three, or 78.2 per cent, when injected into the rabbit's testis in amounts of 2.0 cc. produced syphilitic orchitis.

Within recent years it has been demonstrated that the dissemination of spirochetes in the blood may occur in man even before the appearance of any clinically detectable lesion of syphilis.² In one instance the blood of a donor transmitted a virulent infection to the recipient twenty days before the appearance of a chancre on the penis of the donor and at a time when the serologic tests for syphilis on the donor's blood were negative.³

In 1906 Hoffman first found that the cerebrospinal fluid of a syphilitic man was infectious in the ape.⁴ Since then several studies have shown the presence of *T. pallidum* in the spinal fluid of man during the early stage of syphilis when the fluid was normal on examination by the usual laboratory tests. In three such studies in which the technic of testicular inoculation of the rabbit was used from 15 to 20 per cent of the inoculations gave positive results.⁵⁻⁷ In each case the spinal fluid was apparently normal with respect to cells,

protein, complement fixation and colloidal gold or mastic reaction.

In the last investigation of the problem by Chesney and Kemp the spinal fluids of thirty-four patients were studied.⁸ All patients had one or more clinical signs of early syphilis as well as positive serologic tests on the blood. None had any demonstrable abnormality of the spinal fluid nor did they have any physical sign of neurologic disease. The duration of infection was from three to six months, and secondary manifestations of the disease had been present for from one day to ten weeks. Nine of the patients were white and twenty-five were Negroes; eighteen were males and sixteen were females.

Positive animal inoculations were obtained with the spinal fluid of five, or 14.7 per cent, of the thirty-four patients. Only fluids with cell counts below 9 per cu. mm. were used. All other tests were negative, including complement fixation which was made with 1.0 cc. of spinal fluid. From 0.75 to 3.0 cc. of fluid were used for the inoculation of each rabbit. There was no observable relation between the occurrence of positive inoculations and any particular type of secondary clinical phenomenon of the disease.

As dissemination of the organisms by the blood takes place very soon after infection it must be assumed that invasion of the central nervous system likewise occurs early in the infection. It is obvious that once *T. pallidum* enters the blood stream it neces-

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sarily is carried to the brain and spinal cord and to the meninges. Just how soon and with what frequency the organisms leave the blood to become localized in the extravascular tissues of the nervous system is unknown. Some indication of this may be obtained by the frequency with which *T. pallidum* is present in the cerebrospinal fluid concurrently with its presence in the blood stream early in the disease. It is with this aspect of the problem that we are concerned.

The study which this paper reports was made in Peiping, China, on Chinese patients observed at the Peiping Union Medical College during the years from 1933 to 1941 inclusive. There was a total of fifty patients; however, the animals inoculated with material from four of the patients were casualties of war and no information concerning them is available. This leaves to be described the results of the study on the blood and spinal fluid of forty-six patients, of whom thirty-eight were males and eight were females.

At the time the inoculations were made all patients presented active signs of secondary syphilis and thirteen also had a primary chancre. There were localizations of disease in the integumentary system in forty-four patients and in the skeletal system in fourteen patients. One patient also had iridocyclitis and another had laryngitis. In no case was there any sign of neurologic disease. The complement fixation (Kolmer) and flocculation (Kahn) tests were positive in all patients. In twenty-nine cases dark field examination of cutaneous lesions was positive for *T. pallidum*. In the remaining patients the lesions were not suitable for dark field examination or no organisms could be found.

Forty patients had received no treatment for syphilis. There were six who had been treated at the time of the chancre with from one to three injections of neoarsphenamine. Subsequently, at intervals of from two to sixteen months all six patients developed a clinical relapse in the integumentary system and, in addition, three patients also had le-

sions of the skeletal structures and one had an iridocyclitis. Four of the six patients had minimal abnormalities of the spinal fluid but no anatomic sign of neural disease. All the clinical relapses were in the males. Virulent organisms were isolated from the blood of each patient with clinical relapse and from the spinal fluid of two patients, each with minimal abnormalities of the fluid.

METHOD OF INOCULATION

For the purpose of isolating *T. pallidum* from the blood and spinal fluid the following method was employed: Venous blood was withdrawn from each patient and immediately 1.0 cc. of blood was injected into each testis of two rabbits. In like manner and in the same amount two rabbits were inoculated with spinal fluid. The inoculated animals were observed at frequent intervals of time, never less than once a week, for ninety days or until signs of orchitis developed. Upon the appearance of orchitis material aspirated from the testis was examined for the presence of *T. pallidum* by dark field illumination. An inoculation was considered positive only when treponemes were found by this technic.

When no organisms could be demonstrated microscopically in the enlarged testis, the testis was removed aseptically, emulsified in a sterile isotonic solution of sodium chloride and 1.0 cc. of the emulsion injected into one testis of each of two rabbits. These animals were observed for at least ninety days before being discarded as normal.

In the event that no orchitis developed after a period of ninety days in the animals originally inoculated with blood or spinal fluid, both popliteal lymph nodes were removed aseptically under ether anesthesia and emulsified in sterile isotonic sodium chloride solution. The entire emulsion was divided and one-half was injected into one testis in each of two rabbits. These animals were in turn observed for at least ninety days or until orchitis developed.

In two instances in which animals of the first transfer developed doubtful evidence of syphilis the involved testis was removed and emulsified and 1.0 cc. of the emulsion injected into a testis of each of another two rabbits.

When the animals inoculated with blood or spinal fluid failed to develop orchitis, the chances

of demonstrating organisms by transfer of tissues were small. In fourteen cases in which either testis or lymph node was transferred from rabbits inoculated with blood only two resulted in establishing a demonstrable infection in the rabbit. Of thirty-seven transfers from rabbits

TABLE I
PERIOD OF INCUBATION OF SYPHILIS IN RABBITS INOCULATED
WITH BLOOD OR SPINAL FLUID

Incubation Period, Days	Animals Infected Inoculum	
	Blood No.	Spinal Fluid No.
30-39	1	0
40-49	10	0
50-59	23	1
60-69	10	4
70-79	4	1
80-89	1	1
90-99	1	0
Total	50	7

inoculated with spinal fluid and failing infection only three tissue transfers gave positive results. In one of these cases organisms were observed only after the second transfer of testicular material. The animal of the original inoculation had developed orchitis from which no *T. pallidum* could be found on dark field examination.

RESULTS OF INOCULATIONS

Infectivity of Blood. The blood from forty-six patients was tested for infectivity. Thirty-five, or 76.1 per cent, of the inoculations produced an infection in rabbits. The original inoculation gave positive results in thirty-three cases. The period of incubation of the disease in these animals is shown in Table I.

Positive inoculations were equally distributed between male and female patients. All patients in clinical relapse had infectious blood.

The distribution of positive inoculations with respect to the duration of infection in the patient, as measured from the appearance of the chancre, is given in Table II. The blood of one female patient was in-

fectious in the rabbit ten months following the chancre. In this case condylomatous lesions of the skin had been present for seven months at the time the inoculation was made. In another case, that of a male patient who was in clinical relapse, the blood

TABLE II
DISTRIBUTION OF POSITIVE INOCULATIONS AND ABNORMAL
SPINAL FLUIDS ACCORDING TO THE DURATION
OF SYPHILIS IN THE PATIENT

Duration of Infection, Mo.	Cases No.	Inoculations		Status of Spinal Fluid		
		Blood Positive No.	Spinal Fluid Positive No.	Normal No.	Abnor- mal No.	Bloody No.
1-2	14	10	0	12	2	0
3-4	15	12	4	10	3	2
5-6	5	5	2	3	1	1
7-8	5	4	3	3	2	0
9-10	1	1	0	1	0	0
11-12	1	0	0	1	0	0
13-	1	1	0	1	0	0
Unknown	4	2	0	4	0	0
Total	46	35	9	35	8	3

was infectious thirty-six months following appearance of the chancre and sixteen months after administration of three doses of neoarsphenamine. The spinal fluid of the two patients was normal and did not infect any rabbits. There were six patients with dark field positive lesions of the skin whose blood did not transmit syphilis.

Infectivity of Cerebrospinal Fluid. The spinal fluids of forty-six patients were transferred to the testes of rabbits. There were nine, or 19.6 per cent, positive inoculations all from the fluids of male patients. In seven instances the animals directly inoculated with spinal fluid developed syphilis in from fifty-six to eighty-two days after the inoculation. (Table I.)

Of the forty-six spinal fluids which were examined thirty-five were normal to routine laboratory tests, including the cell count, protein content, and complement fixation and colloidal mastic reactions. The remainder showed minimal abnormalities in the number of cells and in the content of protein except that three fluids also gave a positive colloidal mastic reaction and one a weakly positive complement fixation reac-

tion (2 plus in 0.5 cc. of fluid). Cell counts above 10 per cu. mm. with or without an increase of protein or above 5 per cu. mm. with an increase of protein were considered abnormal. Five of the normal and four of the abnormal spinal fluids produced syphi-

TABLE III
DISTRIBUTION OF POSITIVE INOCULATIONS AND ABNORMAL SPINAL FLUIDS ACCORDING TO DURATION OF SECONDARY MANIFESTATIONS OF SYPHILIS IN PATIENTS

Duration of Secondary Lesions Wk.	Cases No.	Inoculations		Status of Spinal Fluid		
		Blood Positive No.	Spinal Fluid Positive No.	Normal No.	Abnormal No.	Bloody No.
1-2	15	11	2	13	2	0
3-4	9	7	0	5	3	1
5-6	2	2	1	2	0	0
7-8	13	9	4	7	4	2
9-10	0	0	0	0	0	0
11-12	2	2	2	1	1	0
13-14	0	0	0	0	0	0
15-16	1	1	0	1	0	0
17-18	0	0	0	0	0	0
19-26	0	0	0	0	0	0
27-28	1	1	0	1	0	0
29-	1	0	0	1	0	0
Unknown	2	2	0	1	1	0
Total	46	35	9	32	11	3

litic orchitis in rabbits. Among the infectious abnormal fluids was the one showing the greatest deviation from normal.

There was no significant correlation between spinal fluids which were infectious for animals and any particular kind of clinical lesion. The nearest approach to such a relationship was in the patients with alopecia. There were ten cases of alopecia among the forty-six patients in the series. Four of the ten patients showing a loss of hair had infectious spinal fluids. In other words, 40 per cent of patients with alopecia and 13.8 per cent of those with no alopecia had fluids which established an infection in rabbits. The difference of 26.2 per cent, however, is not statistically significant, being within the range of sampling error ($\frac{x}{\sigma} = 1.59$).

There has been one previous report on a study of the cerebrospinal fluid in syphilitic Chinese patients. The study was made dur-

ing 1931 to 1932 by Pearce, Hu and Mu at the Peiping Union Medical College.⁹ It is of interest to observe that in none of forty patients who were studied was the spinal fluid infectious in rabbits. Included in the number examined were ten patients with early active manifestations of syphilis who had never been treated for this disease. All had normal spinal fluids. There were also five patients in neurorelapse, three of whom showed an elevated cell count in the spinal fluid. The technic of inoculation, the size of the inoculum and the period over which the animals were observed conformed to the practice in the present study. Both studies were made in the same laboratory. On the basis of our experience one might have expected to find that two or three of the spinal fluids were infectious.

Relative Infectivity of Blood and Spinal Fluid. From the results of the inoculations it is apparent that infection of the blood in early syphilis does not indicate infection of the spinal fluid. However, infection of the spinal fluid is accompanied by infection of the blood. At least this was true of all patients in this study who had infectious spinal fluids.

It is not to be assumed that the results of inoculation are absolute in their indication of the presence of organisms in either the blood or the spinal fluid. The relative probability of infectivity of the blood and spinal fluid is unknown. Under optimal conditions one is inclined to believe that there are probably more treponemes per unit volume in the blood than in the spinal fluid. The infectivity of these tissues in any case would depend primarily upon the number of organisms present and upon the susceptibility of the rabbit to the first inoculation with organisms unaccustomed to the new host. It might be suspected that the blood of all patients in the active secondary stage of syphilis carries spirochetes although it is possible that the period of greatest infectivity precedes the appearance of metastatic lesions.

If it is assumed that the blood of patients whose infection is not over two months'

duration contains a reasonable number of organisms and is infectious, the blood of all fourteen patients in this study in this period of the disease should have produced syphilis in the inoculated rabbits. As it was only

number of positive inoculations would be twelve, or 26 per cent, of all the tested fluids. This theoretical figure may not be too inaccurate since there were three fluids with minimal abnormalities in the number

TABLE IV
SUMMARY OF CLINICAL AND LABORATORY DATA ON PATIENTS WITH SECONDARY SYPHILIS WHOSE BLOOD AND SPINAL FLUID WERE TESTED FOR INFECTIVITY IN RABBITS

Case No.	Sex	Age Yr.	Duration of Infection Mo.	Duration of Secondary Lesions Wk.	Localization of Lesions			Dark Field Examination	Previous Treatment Arsenical Injections No.	Blood	Serology Spinal Fluid				Animal Inoculation	
					Skin	Hair	Bone				Cells cu.-mm.	Protein	WaR 0.5 cc.	C.M.-R.	Blood	Spinal Fluid
1	M	32	3	2	+	+	-	+	-	+	2	-	-	-	+	+
2	M	30	8	8	+	+	+	+	-	+	34	-	-	+	+	+
3	M	19	4	12	+	-	-	+	-	+	0	-	-	-	+	+
4	M	20	8	12	+	+	-	+	2 (8 mo.)	+	8	+	-	-	+	+
5	M	25	7	8	+	+	+	+	-	+	4	-	-	-	+	+
6	M	43	3	8	+	-	-	+	-	+	12	-	-	-	+	+
7	M	27	5	2	+	-	-	N.E.	-	+	6	-	-	-	+	+
8	M	31	6	8	+	-	-	N.E.	1 (5 mo.)	+	16	+	-	+	+	+
9	M	32	3	6	+	-	+	+	-	+	4	+	-	-	+	+
10	M	31	1	1	+	-	-	+	-	+	2	-	-	-	+	-
11	M	33	36	8	+	+	-	+	3 (16 mo.)	+	4	-	-	-	+	-
12	M	20	3	2	+	-	-	+	-	+	2	-	+	+	+	-
13	M	22	6	2	+	-	-	-	-	+	4	-	-	-	+	-
14	M	46	6	8	+	-	-	-	-	+		Bloody	+	-
15	M	23	2	?	+	-	-	N.E.	-	+	1	-	-	-	+	-
16	F	20	1½	2	+	-	-	+	-	+	2	-	-	-	+	-
17	M	57	2	1	+	-	-	-	-	+	1	-	-	-	+	-
18	M	32	2½	2	+	-	-	+	-	+	4	-	-	-	+	-
19	M	32	3	3	+	-	+	N.E.	1 (2 mo.)	+	4	+	-	-	+	-
20	M	21	3	4	+	-	+	+	1 (2 mo.)	+		Bloody	+	-
21	M	26	3	3	+	-	+	+	2 (2 mo.)	+	6	+	-	-	+	-
22	M	24	6	4	+	+	-	+	-	+	6	-	-	-	+	-
23	M	26	2	2	+	-	+	-	-	+	4	-	-	-	+	-
24	M	13	5	12	+	+	-	+	-	+	0	+	-	-	+	-
25	M	29	3	2	+	-	+	N.E.	-	+	7	-	-	-	+	-
26	F	20	?	8	+	-	-	+	-	+	0	-	-	-	+	-
27	M	26	2	4	+	-	-	+	-	+	9	-	-	-	+	-
28	F	36	7	4	+	-	-	+	-	+	21	-	-	-	+	-
29	F	51	4	8	+	-	+	+	-	+	14	-	-	-	+	-
30	M	26	3	6	+	-	-	+	-	+	2	-	-	-	+	-
31	M	36	1	?	+	-	-	N.E.	-	+	4	+	-	+	+	-
32	M	27	4	4	+	-	+	N.E.	-	+	0	-	-	-	+	-
33	F	35	10	28	+	-	-	+	-	+	4	-	-	-	+	-
34	F	17	?	8	+	-	-	+	-	+	0	-	-	-	+	-
35	M	31	1	2	+	-	-	-	-	+	0	-	-	-	+	-
36	M	16	2	4	+	+	-	+	-	+	2	-	-	-	-	-
37	M	19	4	8	+	+	-	-	-	+		Bloody	-	-
38	M	20	3	8	+	+	+	+	-	+	4	+	-	-	-	-
39	M	25	2	4	+	-	+	+	-	+	8	+	N.D.	N.D.	-	-
40	F	20	?	7	-	-	+	N.E.	-	+	6	-	N.D.	N.D.	-	-
41	M	22	2	2	-	-	-	+	-	+	4	-	-	-	-	-
42	M	25	1	1	+	-	-	-	-	+	8	+	-	-	-	-
43	M	29	4	2	+	-	+	-	-	+	4	-	-	-	-	-
44	M	27	8	2	-	-	+	N.E.	-	+	4	-	-	-	-	-
45	F	17	?	8	+	-	-	+	-	+	10	-	-	-	-	-
46	M	22	12	44	+	-	-	+	-	+	0	-	-	-	-	-

WaR = Wassermann reaction (Kolmer Technic) with 0.5 cc. of spinal fluid. C.M.R. = Colloidal gum mastic reaction.

N.E. = Not examined. N.D. = No data. Under "Previous Treatment" the figures in parentheses show the number of months elapsing between treatment and animal inoculation.

ten of the specimens did so. This would suggest that the experimental error was about 25 to 30 per cent. Assuming further that the same error would apply to the infectivity of the spinal fluid, the expected

of cells and in the content of protein that did not infect rabbits.

This study offers no evidence as to the time after infection when invasion of the spinal fluid occurs. It is of interest, however,

that none of the fourteen patients with infections of less than three months' duration had spinal fluid which was infectious in the rabbit while four of fifteen patients with infections of from three to four months' duration had infectious fluids.

It is to be observed in Table III that in two patients with secondary manifestations of not over two weeks' duration the spinal fluid was found to contain virulent organisms.

SUMMARY

The blood and cerebrospinal fluid of forty-six Chinese patients in the active secondary stage of syphilis were inoculated into rabbits. The blood proved to be infectious in thirty-five, or 76.1 per cent, and the spinal fluid in nine, or 19.6 per cent, of the cases. There was no correlation between a particular clinical lesion and infectivity of the spinal fluid although the frequency of positive inoculations in patients with alopecia approached statistical significance. (Table IV.)

No organisms were isolated from the spinal fluid of patients whose infections were of less than three months' duration. All

patients with infectious spinal fluids also had virulent organisms in their blood.

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Penicillin in Oil and Beeswax in the Treatment of Syphilis in Clinic Patients*

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THE successful treatment of syphilis within the last thirty-five years has been greatly hampered by the fact that the various drugs used had to be given over a period of many months in order to be effective. A great proportion of patients lapsed from this type of prolonged treatment before any therapeutic effects were ever obtained. In Kampmeier's book, "Essentials of Syphilology," Alvin E. Keller states that "only 20 to 30 per cent of all patients receiving anti-syphilitic treatment received as many as 20 injections of an arsenical preparation and 20 injections of a heavy metal." This fact has been confirmed by various other authors.

Ever since penicillin was accepted as an efficient and the least toxic of all anti-syphilitic agents, it has been the aim of syphilologists to develop an effective wholly ambulatory treatment schedule. A step forward in this direction was made when Romansky's formula became available, ensuring therapeutic levels in the vast majority of patients for at least a twenty-four-hour period following a single injection of 300,000 units of POB. This method of administering penicillin has proved to be of considerable value, particularly to communities where intensive treatment centers or other public health facilities are not readily available.

The Clinic Section of the Chicago Venereal Disease Control Program undertook to determine the cooperativeness of clinic patients in completing a short term method of treatment with penicillin in oil and beeswax on an ambulatory basis. The

study was begun in February, 1947, and was first intended to include only untreated or insufficiently treated late latent syphilis cases. However, soon after the study was started other types of syphilis such as early latent syphilis, asymptomatic and symptomatic neurosyphilis without frank psychosis, cardiovascular syphilis, congenital syphilis, syphilis in pregnancy and even a number of early infectious cases were included in this study. The latter group consisted of patients who were unable for various reasons to enter the hospital for intensive therapy. All patients placed on penicillin therapy from February, 1947, to February, 1948, are included in this report. This group of patients constitutes approximately 30 per cent of all types of syphilis cases diagnosed by the Chicago Health Department clinics.

In the beginning of the study of late latent syphilis, patients who either had no treatment or less than twenty arsenicals and twenty bismuth injections were included in the series. After a personal interview with the caseworker, who pointed out the advantages of this new treatment schedule and the importance of regular attendance, the patients received daily injections of 450,000 units of penicillin in oil and beeswax over a period of ten treatment days (omitting Saturdays and Sundays), a total of 4,500,000 units. Exceptions: (1) the treatment schedule for group 2 and group 3 spinal fluid changes in neurosyphilis, as defined by J. E. Moore in his book, "The Modern Treatment of Syphilis" (1947 edition), was increased to fifteen treatment days, or 6,750,000 units and (2) patients

* From the Venereal Disease Control Program of the Chicago Health Department, in cooperation with the United States Public Health Service.

with cardiovascular syphilis were treated with 100,000 units per day for three days, increased to 200,000 units on the fourth and fifth treatment days and to 300,000 units from the sixth to the fifteenth day.

the clinics are of the late latent type. Neurosyphilis is the next largest group in this study with 24.9 per cent. This group constitutes only 3 per cent of the total syphilitic cases diagnosed during 1947. It is of interest to

TABLE I
SYPHILIS PATIENTS UNDER TREATMENT WITH PENICILLIN IN OIL AND BEESWAX

Diagnosis	Total		Male				Female			
	No.	Per Cent	White	Color-ed	Total	Per Cent	White	Color-ed	Total	Per Cent
Primary syphilis	4	0.4	2	2	4	0.8	0.0
Secondary syphilis	2	0.2	...	1	1	0.2	..	1	1	0.2
Early latent syphilis	12	1.2	2	3	5	1.2	1	6	7	1.4
Late latent syphilis	596	59.6	54	228	282	58.4	27	287	314	60.7
Neurosyphilis	249	24.9	58	108	166	34.4	35	48	83	16.0
Cardiovascular syphilis	12	1.2	1	5	6	1.2	..	6	6	1.2
Congenital syphilis	32	3.2	2	17	19	3.9	1	12	13	2.5
*Syphilis complicated by pregnancy	93	9.3	1	92	93	18.0
Total	1000	100.0	119	364	483	100.0	65	452	517	100.0

* Early latent syphilis	50
Late latent syphilis	34
Cardiovascular syphilis	1
Congenital syphilis	8
Total	93

All patients were instructed to return daily for their prescribed treatment except on Saturdays and Sundays but they were permitted to lapse for two days between treatment days before the lapse was considered permanent. Patients who attended the clinic three or more times a week, completing ten injections within twenty-one days, were considered in this study to have completed their treatment satisfactorily. If a patient lapsed for more than two days between treatment, he was re-instituted on the prescribed treatment schedule.

A statistical tabulation of 1,000 patients so treated with penicillin in oil and beeswax on an ambulatory basis is herewith presented. Table I shows a classification of cases into the various types of syphilis. The largest group constitutes late latent syphilis with 59.6 per cent of all patients although only 23 per cent of all syphilis cases diagnosed in

note that in the group of 1,000 patients there is a slightly larger proportion of female patients, namely, 51.7 per cent, while in the total group of diagnosed syphilis cases we have approximately 47 per cent of female patients. This, however, is not a significant difference.

In both the cases of this study and the total number of syphilis cases diagnosed in the clinics during 1947, approximately 18 per cent were white.

A breakdown in age groups of all patients in this study is shown in Table II. The median age of the syphilis patients treated with POB is thirty-eight years, while the median age of all syphilis patients diagnosed is twenty-five years of age. We find, therefore, that the color and sex rate in this study group and in the total group of patients diagnosed during the study period show no appreciable difference. The dis-

crepancy in the median age between these two groups is explained by selection of the latent syphilis cases for this study.

As shown in Table III, of a total of 1,000 patients 859 or 85.9 per cent completed their prescribed treatment, and 141 patients

In reviewing the charts of those patients who lapsed at one time or another, it was found that the reasons of their lapsing were given as follows: seventeen patients experienced a severe rash, eleven complained of sore hips; among the remaining 185

TABLE II
SYPHILIS PATIENTS TREATED WITH PENICILLIN IN OIL AND BEESWAX

Diagnosis	Age Groups—Years							Total
	2-9	10-19	20-29	30-39	40-49	50-55	Over 55	
Primary syphilis.....	0	0	3	1	0	0	0	4
Secondary syphilis.....	0	0	1	1	0	0	0	2
Early latent syphilis.....	0	1	6	4	1	0	0	12
Late latent syphilis.....	0	0	90	244	174	63	25	596
Neurosyphilis.....	0	0	30	65	92	39	23	249
Cardiovascular syphilis.....	0	0	1	3	4	3	1	12
Congenital syphilis.....	1	24	6	0	1	0	0	32
Syphilis complicated by pregnancy.....	0	4	55	33	1	0	0	93
Total (all forms by age groups).....	1	29	192	351	273	105	49	1,000

TABLE III
SYPHILIS PATIENTS PLACED UNDER TREATMENT AND COMPLETING PRESCRIBED TREATMENT SCHEDULE, CLASSIFIED ACCORDING TO SEX AND TYPE OF SCHEDULE*

	Total			Ten-day Schedule			Fifteen-day Schedule		
	Placed under R	Completed R	Per Cent Completed R	Placed under R	Completed R	Per Cent Completed R	Placed under R	Completed R	Per Cent Completed R
Male.....	483	406	84.1	334	281	84.1	149	125	83.9
Female....	517	453	87.6	433	386	89.1	84	67	79.8
Total...	1,000	859	85.9	767	667	87.0	233	192	82.4

* Includes reinstatements after lapse to first regimen.

discontinued for various reasons. There were 767 patients on the ten-injection-day schedule, of whom 87.0 per cent completed the course and 233 on the fifteen-injection-day regimen, of whom 82.4 per cent finished their prescribed course. Although 141 patients failed to complete treatment, there were 213 patients who lapsed from the first regimen. However, seventy-two of the eighty-eight patients (81.8 per cent) were reinstated and finished a new treatment course.

patients there were sixty patients who gave intercurrent personal or familial illness as the reason for discontinuance of treatment, while 125 patients disappeared without indicating the cause.

SUMMARY AND CONCLUSIONS

1. The clinic attendance of 1,000 syphilitic patients placed on an ambulatory ten- or fifteen-day-treatment schedule of penicillin in oil and beeswax is recorded.

2. Eighty-five and nine-tenths per cent

of all patients completed their prescribed treatment regimen; divided according to the two different treatment schedules employed, 87.0 per cent completed their ten-injection-day regimen and 82.4 per cent completed their fifteen-day schedule.

3. Twenty-eight patients discontinued or lapsed treatment because of local or allergic manifestations and sixty patients failed to complete treatment because of intercurrent illnesses either personal or within their families; 125 patients disap-

peared from observation for unknown reasons.

4. This form of therapy is far superior as regards clinic attendance compared with the 30.0 per cent attendance recorded for long-term chemotherapy.

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Auricular Flutter in Association with Myocardial Infarction*

Its Prognosis and Management

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AURICULAR flutter is an arrhythmia rarely encountered in association with myocardial infarction. It was found in 3 (1 per cent) of 300 patients reported by Master¹ and in 5 of 208 patients (2.5 per cent) in Rosenbaum and Levine's³ series. Recently Chambers² recorded three instances in one hundred patients with myocardial infarction. Among 1,247 patients studied at the Los Angeles County Hospital it was discovered in nineteen instances (1.5 per cent). In the same group auricular fibrillation was found in eighty-four instances (7.7 per cent). The burden imposed by auricular flutter ordinarily depends upon the concomitant state of the heart itself as well as the nature of the flutter. The faster the ventricular rate and the longer the persistence of the tachycardia, the greater the burden and the greater the hazard. In association with the acute cardiac damage of myocardial infarction, auricular flutter with tachycardia should constitute a serious handicap.

These nineteen cases represent the material used in this study. We were concerned chiefly with the prognostic importance of auricular flutter and its management. We have analyzed this series with these two considerations particularly in mind.

Mortality. Twelve of the nineteen patients (63 per cent) died during the period of hospitalization. The mortality of the whole group of 1,247 patients was 51.5 per cent. Of the twelve patients who died, in

eight the auricular flutter persisted until death, seven with a ventricular rate of 140 or more. (Table I.) The majority (five of the eight) died within twenty-four hours of the onset, with ventricular rates over 140. One died two days, one four days and one

TABLE I
TYPE OF DEATH IN EIGHT PATIENTS WITH AURICULAR FLUTTER AND MYOCARDIAL INFARCTION

Cause of Death	Ventricular Rate	Comments
Acute congestive failure.	150 for 4 days	Previous infarction
Sudden death.....	120 for 2 days	Previous infarct, intraventricular block
Sudden death.....	150 for 1 day	Previous infarct
Sudden death.....	160 for 1 day	Previous infarct, intraventricular block
Acute congestive failure.	140 for 5 days	"Enlarged heart" before
Acute congestive failure.	142 for 1 day	Intraventricular block, angina before attack
Acute left ventricular failure.....	140 for 1 day	
Acute congestive failure.	140 for 1 day	

five days after the onset. Five of the eight deaths were attributed to acute congestive failure, three were sudden deaths presumably due to a fatal ectopic ventricular rhythm. There is little doubt that the persisting rapid ventricular rate was the immediate cause of death in these patients. Among the four patients who died despite a return to normal rhythm the causes of death were as follows: (1) Acute congestive failure. In one patient the ventricular rate had remained at 160 for fourteen days before the return to normal rhythm. The prolonged tachycardia induced death even

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though sinus rhythm returned. (2) Sudden death. One patient died suddenly eight days after a return to normal rhythm. The auricular flutter had lasted only one day and was associated with a normal ventricular rate. It probably did not influence the

TABLE II
RESPONSE TO MEDICATION IN AURICULAR FLUTTER
ASSOCIATED WITH MYOCARDIAL INFARCTION

Medication	No. of Patients	No. Returning to Normal Rhythm
No medication	8	5
Digitalis and quinidine	4	2
Digitalis alone	5	2
Quinidine alone	2	2

death. (3) Pneumonitis. One patient died of supposed pneumonia; auricular flutter with a ventricular rate of 120 had lasted two days. This patient had had a previous myocardial infarction three years before. The auricular flutter can be implicated as a contributory cause of death. (4) Myocardial infarction. The fourth patient died of a second infarct. The auricular flutter had occurred twice, disappearing each time within twenty-four hours. It apparently was of negligible importance in the cause of death, merely reflecting the severe cardiac damage. From these data it would appear that auricular flutter was responsible for at least nine of the twelve deaths due to the burden of the associated tachycardia. Death in the other three patients probably would have occurred even if auricular flutter had not been present.

Persistence of the Auricular Flutter. In eight patients arrhythmia persisted; in eleven patients it disappeared.

Correlation of Mortality with Persistence of the Auricular Flutter. All of the eight patients with persistence of the auricular flutter died. Of the eleven patients in whom the arrhythmia disappeared four died (36.3 per cent), seven lived.

Correlation of the Ventricular Rate with Mortality. Of the thirteen patients with ventricular rates of 120 or more eleven died (85.7 per cent). Of the six with a

ventricular rate of 100 or less one died (16.6 per cent).

Correlation of Ventricular Rate with Subsequent Persistence or Disappearance of the Arrhythmia. Only five of the thirteen with ventricular rates over 120 returned to normal rhythm. Of six with ventricular rates below 100 all returned to normal rhythm.

Correlation of Persistence with the Severity of the Heart Disease. Of the eight patients with persistence of arrhythmia five gave a history suggestive of previous infarction. This was confirmed in four necropsies obtained in the eight patients. A sixth patient had had a previously enlarged heart. Six (or 75 per cent) gave, therefore, a history of previous heart trouble. Of the eleven in whom the arrhythmia disappeared only four (33.3 per cent) gave histories of previous cardiovascular disease.

RESPONSE OF AURICULAR FLUTTER TO DIFFERENT TREATMENT

Response of the auricular flutter to varying treatment is shown in Table II. Few deductions are justified from the data because dosage of the drugs was not optimum. Among the five patients given both digitalis and quinidine the dosage varied considerably and probably was not adequate for both of the drugs. In only three patients was the dosage sufficient to justify an analysis of the response. Of the five patients given digitalis alone in only two was the dosage adequate. In only one of these patients did the rhythm return to normal. In the two patients given quinidine alone the return to normal rhythm might easily have been spontaneous. The dosage of quinidine was not optimum.

CASE REPORTS

CASE No. 707069. A man, aged seventy-five with no preceding cardiovascular history, had an attack of chest pain March 5, 1940. An electrocardiogram March 6, 1940, revealed the pattern of anterior infarction. The following day auricular flutter with a ventricular rate of 160 developed. Digitalis (powdered leaf pills) was given in successive daily doses of 13½ gr.,

6 gr., 3 gr. and then $1\frac{1}{2}$ gr. daily. There was no change in the auricular flutter for eleven days, from March 7, 1940 to March 18, 1940. Quinidine was then given in doses varying from 40 to 54 gr. daily. Sinus rhythm returned four days later, on March 22, 1940, but the patient died the same day of acute left ventricular failure.

This illustrates the difficulty at times of affecting auricular flutter at all. It illustrates also the difficulty of affecting some patients quickly even with large doses of digitalis and quinidine. This patient had a ventricular rate of 160 from March 7, 1940 to March 21, 1940 (fourteen days). Undoubtedly this tachycardia was the cause of death. In retrospect, we could wish that quinidine had been given sooner. Had it been started on the first day the ventricular rate possibly could have been controlled sooner.

CASE No. 819627. A man, aged seventy-two with previous known hypertensive cardiovascular disease, was admitted October 6, 1941, with a history of myocardial infarction occurring three weeks before. The electrocardiogram confirmed this diagnosis and showed auricular flutter, with a ventricular rate of 150 and 2:1 auriculoventricular block. Lanatoside C was given intravenously (4 cc. of cedilanid). Two days later there was normal rhythm. On October 10, 1941, digitalis by mouth, ($1\frac{1}{2}$ gr. of powdered leaf) was started daily and also quinidine in 6-gr. doses four times daily. Five days later, October 15, 1941, despite this medication, impure auricular flutter appeared. Digitalis was increased to $1\frac{1}{2}$ gr. four times daily and quinidine was continued 3 gr. four times daily. The next day normal rhythm returned and continued for one month at which time the patient developed a second infarct with an electrocardiographic pattern of a posterior lesion. He died suddenly the same day. Therapy for the flutter, however, may be considered satisfactory in this case inasmuch as death was not ascribed to the arrhythmia.

Auricular Flutter and Complete Auriculoventricular Block in Association with Myocardial Infarction. The simultaneous occurrence of auricular flutter and complete auriculoventricular block in any heart condition is unusual. (Table III.) Jourdonais and Mosen-

thal⁴ reviewed the twenty-nine reports in the literature of auricular flutter associated with complete auriculoventricular block and recorded another instance. Nearly all patients were middle-aged men with arteriosclerotic heart disease. DeMoura⁵ recently recorded an instance in a thirty year old male with rheumatic heart disease. The flutter and complete block persisted until death. No necropsy was obtained. De Gregorio and Crawford⁶ recorded two more instances, one patient had suffered a recent coronary occlusion. Gray and Greenfield⁷ reported another case but the necropsy revealed no recent infarction. Miller and Perelman⁸ described a patient with myocardial infarction three years before who developed auricular flutter and complete auriculoventricular block. Katz⁹ shows a tracing of this condition in his book. We wish to describe a patient in whom auricular flutter and complete auriculoventricular block with the Stokes-Adams syndrome occurred coincident with myocardial infarction.

CASE No. 753017. Mr. H. K., eighty-two years old, was admitted May 29, 1941. He had awakened at 5 A.M. very short of breath but with no pain. Physical examination revealed an old man acutely dyspneic and cyanotic, passing into a state of stupor for a short time and then becoming mentally clear. There were occasional mild convulsive movements. The blood pressure was 100 systolic, 60 diastolic. The heart sounds were weak, irregular, with a rate of 30 to 40. An electrocardiogram taken on two occasions, on May 29, 1941, showed auricular flutter and auriculoventricular dissociation. The patient continued to suffer severe convulsive seizures with bradycardia. At times the heart rate would change suddenly to 100. He was given $\frac{3}{8}$ gr. of ephedrine sulfate every four hours day and night from May 29, 1941 to June 2, 1941, and adrenalin, 10 minims, hypodermically for the acute attacks of Stokes-Adams seizures. On June 2, 1941, normal sinus rhythm had returned. There was no return of auricular flutter or heart block. The further course was uneventful. He was discharged on June 26, 1941. He was seen at the orthopedic clinic for an injured leg on September 16, 1941, and had no medical complaints. The

TABLE III
AURICULAR FLUTTER COMPLICATING MYOCARDIAL INFARCTION; ANALYSIS OF NINETEEN OCCURRENCES AMONG 1,247 PATIENTS WITH MYOCARDIAL INFARCTION

Age	Sex	Evidence of Previous Infarct		Previous Cardiovascular History	Other Arrhythmias or Defects	A-V Block and Ventricular Rate	Days after Attack	Days Auricular Flutter Lasted	Did Sinus Rhythm Return	Type of Death	Did Auricular Flutter Cause Death	Medication		Comment
		History	Necropsy									Digitalis	Quinidine	
61	M	Positive	Recent and old infarct	Edema, orthopnea 1½ yr.	V.P.B.	2-1 Aur. rate, 290 Ven. rate, 150	5	4 (until death)	No	Acute congestive failure	Yes, rapid ven. rate	Only maintenance dose	None	Medication inadequate
72	M	Chest pain	Recent and old infarct	Dyspnea, chest pain 1 yr.	i.v. block	Aur. rate, 240 to 360; Ven. rate, 120	7	2 (until death)	No	Sudden death	Yes	After 24 hours 4 cc. cedilanid i.v. plus 6 doses of oral cedilanid	None	
66	F	Chest pain	Recent and old infarct	Chest pain 3 yr.	0	2-1 Aur. rate, 300 Ven. rate, 150	3	1 (died same day)	No	Sudden death	Yes	1½ gr for 4 doses	3 gr. then 6 gr. every 2 hr. for 5 doses	Digitalis not adequate; quinidine adequate
46	M	Positive	Recent and old infarct	Chest pain; high blood pressure	0	3-1 Aur. rate, 480 Ven. rate, 160	3	1 (died same day)	No	Sudden death	Yes	None	None	No time to give adequate amount
52	M	None	No necropsy	Enlarged heart	Sinus tachycardia, 110	2-1 Aur. rate, 280 Ven. rate, 140	11 wk.	5 days (later)	No	Acute congestive failure	Yes	9 gr.	Started after 3 days 6 gr. every hr. for 8 doses	Digitalis not adequate; quinidine started late
34	M	Chest pain 1 yr. before	No necropsy	Chest pain 1 yr. before	i.v. block	2-1 Aur. rate, 290 Ven. rate, 142	2	(Died same day)	No	Acute congestive failure	Yes	None	None	No time to give medication
83	M	None	No necropsy	None	0	2-1 Aur. rate, 280 Ven. rate, 140	9	1 (died next day)	No	Acute congestive failure; ven. fib.	Yes	None	None	Not adequate
68	F	Positive 3 yr. before	No necropsy	High blood pressure 10 yr.; infarct 3 yr. before	Aur. fib.	3-1 Aur. rate, 360 Ven. rate, 120	5 wk.	2 days, then aur. fib. then sinus rhythm	Yes	Pneumonia	No	10½ gr. in 2 days	None	May have been spontaneous
72	M	None	No necropsy	Dyspnea on effort 6 mo; high blood pressure; enlarged heart	i.v. block	2-1 Aur. rate, 280 Ven. rate, 140	21	2 days 1 day	Yes	Second infarct	No	Cedilanid 4 cc. i.v. digitalis 1½ gr. daily orally	3 gr. four times a day	First infarct anterior, second infarct with death posterior (9 wk. later)
57	M	None	No necropsy	None	Aur. fib.	4-1 Aur. rate, 300 Ven. rate, 75	15	1 (died 8 days later)	Yes	Sudden death	No	None	3 gr. for 5 doses	May have been spontaneous

TABLE III (Continued)

Age	Sex	Evidence of Previous Infarct		Previous Cardiovascular History	Other Arrhythmias or Defects	A-V Block and Ventricular Rate	Days after Attack	Days Auricular Flutter Lasted	Did Sinus Rhythm Return	Type of Death	Did Auricular Flutter Cause Death	Medication		Comment
		History	Necropsy									Digitalis	Quinidine	
75	M	None	No necropsy	None	0	Aur. rate, 300 Ven. rate, 160 For 14 days 2-1	2	14	Yes	Acute congestive failure	Yes	24 gr. in 24 hr., then 1½ gr. daily for 10 days	After 10 days 40-54 gr. daily for 4 days	Adequate dosage by usual criteria
48	M	None	Lived 6 mo.	High blood pressure	Aur. fib.	2-1 Aur. rate, 300 Ven. rate, 150	6	1	Yes	Lived 6 mo.	No apparent bad effect	None	None	
55	M	None	Lived	None	A.v. block	Variable Aur. rate, 400 Ven. rate, 80	18	Gone after 19 days	Yes	Lived	No apparent bad effect	None	None	No EKG for 19 days
66	F	None	Lived	None	A.P.B.	2-1 and 3-1 Ven. rate, 145	2	Gone after 9 days	Yes	Lived	No apparent bad effect	None	None	No EKG for 9 days
57	M	None	Lived	Rh. ht. dis.; dyspnea, yr.	0	4-1 Aur. rate, 300 Ven. rate, 75	13	4	Yes	Lived	No, slow ven. rate	28 gr. in 3 days	None	
61	M	None	Lived	None	Sinus tachycardia, 130; transient i.v. block	4-1 Aur. rate, 320 Ven. rate, 85	5	1	Yes	Lived	No, slow ven. rate	None	None	
82	M	None	Lived	None	A.v. block	Complete A.v. block; aur. rate, 220 Ven. rate, 20-50	1	2	Yes	Lived	Lived	None	None	
55	M	None	Lived	Chest pain on exertion	A.P.B.	Variable; aur. rate, 210 Ven. rate, 70	6	1	Yes	Lived	No, slow ven. rate	None	3 gr. three times a day	
51	M	None	Recent infarct	None	0	Aur. rate, 280 Ven. rate, 140	1	1	No	Acute left ven. failure	Yes	4 cc. digilamid i.v.	None	

A.P.T.—auricular paroxysmal tachycardia.
A.P.B.—auricular premature beats.
V.P.B.—ventricular premature beats.
i.v. block—intraventricular block.
Rh. ht. dis.—rheumatic heart disease.
Aur. fib.—auricular fibrillation.
Ven. fib.—ventricular fibrillation.

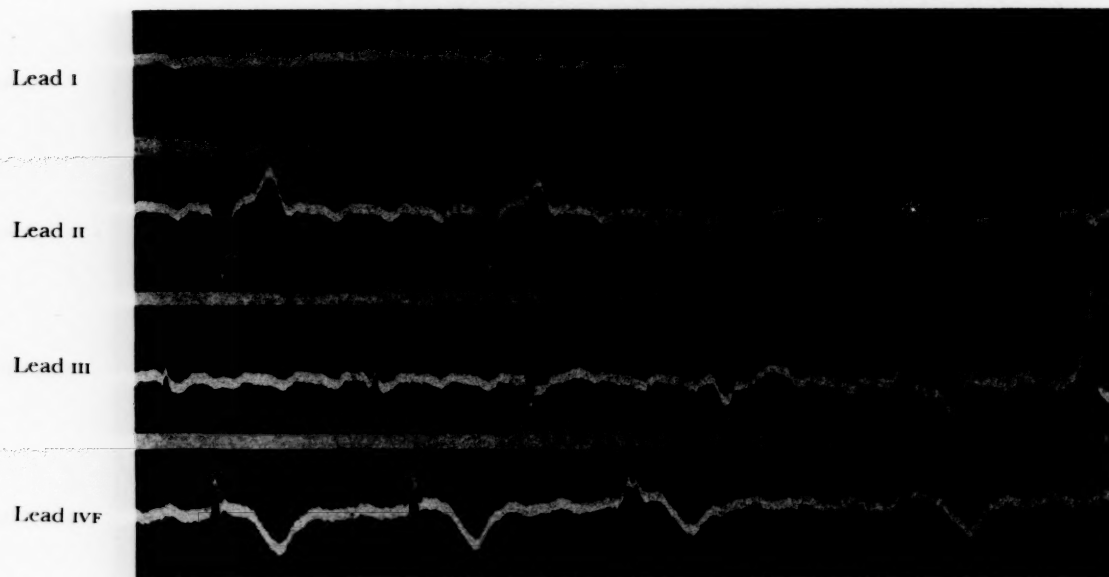


FIG. 1. Auricular flutter May 29, 1941. Complete auriculoventricular block; irregular idioventricular rhythm due to varying foci of ventricular pacemakers; anterior infarction.

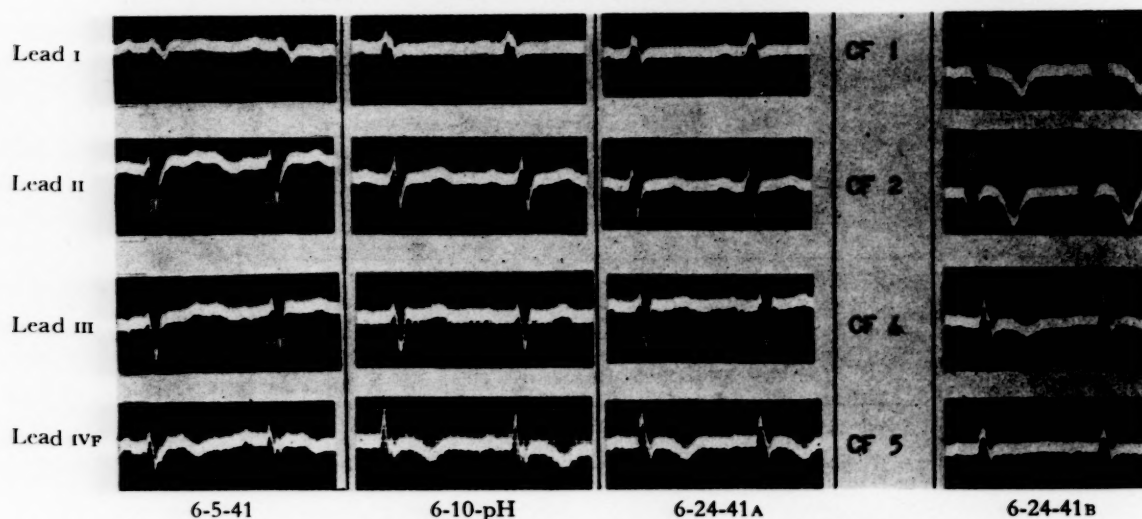


FIG. 2. Serial tracings after return to sinus rhythm; June 5, 1941, sinus rhythm, right bundle branch block; June 10th, sinus rhythm, left bundle branch block with reversal of bundle branch block since previous tracing; T ivf changes progressive; 6-24-41A, sinus rhythm, left bundle branch block; 6-24-41B, T wave inversion most marked in CF₁ and CF₂.

serial electrocardiograms are shown and corroborate the diagnosis of anterior myocardial infarction. (Figs. 1 and 2.)

The occurrence of complete auriculoventricular block and auricular flutter synchronous with an attack of myocardial infarction is extremely rare. Recovery from these complications by a patient eighty-two years old is amazing. The apparent intraventricular block present in the first tracing was not confirmed until the auriculo-

ventricular block was gone and the widened QRS complex persisted. Widened QRS complexes occur commonly in complete auriculoventricular block but are not indicative of associated intraventricular block *per se*. They may indicate merely that the focus for the idioventricular pacemaker is below the bifurcation of the common bundle. Katz⁹ believes a diagnosis of intraventricular block is not justified unless records taken when complete auriculo-

ventricular block is absent show that the condition exists. In the thirty-six records in the literature the QRS complexes were widened in ten instances. An interesting feature in several instances was an apparent reversal at times of the bundle branch block patterns.

AURICULAR FIBRILLATION VERSUS AURICULAR FLUTTER IN MYOCARDIAL INFARCTION

A comparison of the varying effect of auricular fibrillation and auricular flutter as a complication of myocardial infarction is of interest. The two arrhythmias have much in common in their relationship to myocardial infarction, even as they have in relation to other types of heart disease. They usually are a reflection of serious heart damage. If they occur with myocardial infarction, usually they indicate the existence of previous cardiovascular disease. In the group of eighty-four patients with auricular fibrillation discovered in the whole group of 1,247, fifty-eight (69 per cent) gave signs or symptoms of previous cardiovascular disease. In the group of nineteen with auricular flutter there were eleven (58 per cent). In both groups the majority of those in whom the arrhythmia persisted had either a history or necropsy evidence of previous infarction. The relation of the time of onset of the arrhythmia to the time of the attack was interesting and varied in the two arrhythmias. Whereas auricular fibrillation occurred in a large percentage at approximately the same time as the attack (forty-nine of eighty-four patients), auricular flutter occurred after the attack in all patients, in the majority six days or more after the attack.

The difference in the incidence of embolism was interesting but not unexpected. Whereas among those with auricular fibrillation there was a high percentage of pulmonary and systemic embolism, no diagnosis of embolism was made as a complication of auricular flutter. This is in keeping with what is observed in arrhythmias complicating other heart conditions. McMillin and Bellet¹⁰ commented on the

low incidence of embolism accompanying auricular flutter in general and stated that "the weight of evidence indicates that embolism rarely if ever occurs during flutter." The mortality associated with both arrhythmias, if persistent, was very high. Four of fifty-five patients survived, however, in the group which had persistent auricular fibrillation with myocardial infarction. All those patients with persistent auricular flutter died.

COMMENTS

Deductions derived from a small number of observations must be cautiously interpreted. The errors of statistical evaluation of small groups are illustrated in several instances in this study. For instance, of six patients with auricular flutter with a ventricular rate of 100 or less, only one died (16.6 per cent). Erroneously, therefore, it might be considered a good prognostic omen if auricular flutter with a ventricular rate under 100 complicated myocardial infarction since the mortality of the whole group of 1,247 was 51.5 per cent. This inference is obviously untenable. The deductions in this group that would suggest themselves as probably applicable in general are little more than corroborative of prevalent clinical opinion. Auricular flutter is a known concomitant of serious heart disease in general; it is of similar significance in myocardial infarction. The hazard of the arrhythmia is in general proportional to the rate and duration of the associated tachycardia. This is apparently true in relation to myocardial infarction. The three patients with auricular flutter in Chambers² report all recovered. Sinus rhythm returned in all three and in two without medication. The third patient received digitalis. In one the auriculoventricular block was 4:1 with a slow ventricular rate, and in a second the auricular flutter returned to sinus rhythm the second day; so the rate in one was slow and the duration of the tachycardia in the other was short.

In general there usually is little hazard of embolism if auricular flutter occurs. It

would appear that this is true in myocardial infarction. The treatment of auricular flutter is its elimination, with return to normal rhythm, by the use of digitalis and quinidine. This would seem to hold also in the management of auricular flutter in association with myocardial infarction. Mc-Millan and Bellet¹⁰ stress the urgent need for abolishing flutter in certain cases of severe cardiac failure not associated with myocardial infarction. In certain instances they have given massive doses of digitalis and quinidine in view of the relative risk of the disease and of the drugs. Certainly in the instances of myocardial infarction with tachycardia due to auricular flutter reported in this study quick termination of the arrhythmia was an urgent need. Optimum doses of digitalis and quinidine should have been administered early in practically all instances. Digitalization can be rapidly accomplished by use of oral glycosides if the patient is not vomiting. Otherwise, intravenous lanatoside C may be utilized. Only in patients with a normal ventricular rate without congestive heart failure would medication seem unnecessary under these conditions. In such instances there is relatively little burden imposed upon the heart. The six patients with ventricular rates below 100 all returned to normal rhythm, three of them with no drug treatment and five of the six lived.

Tandowsky¹¹ advocates use of quinidine after the auricular flutter has been converted into auricular fibrillation. He agrees, however,* that in the presence of myocardial infarction it is probably desirable to give both drugs simultaneously. There is the possibility that digitalis, if given alone, may produce ectopic ventricular rhythms which quinidine can prevent.

The experience described has suggested a program for future medication. The appearance of auricular flutter with tachycardia as a complication of myocardial infarction will be considered as requiring emergency treatment; the urgency of the need for termination of the tachycardia

* Personal communication.

being indicated by the fact that five patients died within twenty-four hours of the onset. Patients with auricular flutter with a normal ventricular rate without congestive failure will receive no medication. Rapid digitalization with a potent glycoside, such as digitoxin, and simultaneous administration of quinidine will be the program. Our practice is to give six tablets of digitoxin (1.2 mg.) at once and quinidine, 6 gr., every two hours until the arrhythmia is abolished. Digitoxin is continued in 0.2 mg. doses daily. In case the patient is unable to take medication orally lanatoside C may be given intravenously, 4 cc. at once, to be repeated in a few hours. Parenteral quinidine prepared according to the formula of Sturnick et al.¹² can be used. This is an effective method and the problem of absorption is eliminated. We intend not to discontinue quinidine because of rash, nausea without vomiting, headache or dizziness; these are of minor importance in relation to the danger of continuance of the auricular flutter.

CONCLUSIONS

1. Auricular flutter occurred in 19 of 1,247 patients with myocardial infarction studied at the Los Angeles County Hospital.
2. When associated with rapid ventricular rate, the arrhythmia constituted a serious hazard resulting in death in all cases in which it did not terminate soon.
3. A program of management is suggested.

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Review

The Role of Tonsillectomy in the Management of Recurrent Streptococcal Sore Throat, Rheumatic Fever and Glomerulonephritis*

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THE concept that foci of infection frequently cause or influence the course of systemic disease, as propounded by Billings and others, has been questioned in recent years. Reimann and Havens pointed out the fallacies in the original reasoning and concluded that careful examination of the evidence failed to reveal good therapeutic results from removal of chronically infected teeth and tonsils for such diseases as rheumatoid arthritis, peptic ulcer, ulcerative colitis and the like.²¹ Cecil, previously one of the chief proponents of the concept, has since concluded that the ideas originally brought forth no longer can be held.⁴ Irons, on the other hand, has recently defended the teachings of Billings and maintains that in cases of iritis and in certain types of infectious arthritis the removal of such foci often benefits the patient.¹⁰

Closely allied in many respects is the question of the role that tonsillectomy should play in the management of patients with recurrent streptococcal sore throats and with the attendant complications of rheumatic fever and glomerulonephritis. Since the tonsils constitute the major site of parasitism by the beta hemolytic streptococcus, it might be expected that removal

of these organs would diminish the chance of infection and of late non-suppurative complications. The present review is concerned with the available evidence on these points.

Many articles concerned with this subject present data in such a way that definite conclusions cannot be drawn. Carefully chosen control groups and adequate follow-up studies are lacking in many of the reports. Moreover, precise bacteriologic and serologic data are frequently absent. An unpredictable source of error is injected when two groups are studied, one having had tonsils removed, and conclusions are drawn as to the subsequent development of streptococcal disease and its complications. This error can be attributed to the fact that in any group of tonsillectomized patients the incidence of previous streptococcal infections is probably higher than in the general population, hence the indication for operation. Such factors were not taken into consideration in many of the conclusions that have been drawn.

For proper evaluation of these problems it is essential to select a group for study and to follow it with careful clinical, bacteriologic and immunologic observations over a period of years. Reviewing case histories

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without personal observation of the patients concerned is productive of many errors. This review strives to attain a more critical perspective with regard to frequently accepted axioms concerning the management of streptococcal disease and its late complications, and to point out the need for more complete data.

STREPTOCOCCAL SORE THROAT

Removal of the tonsils will obviously decrease the incidence of tonsillitis. However, while this procedure removes from the throat the largest single body of tissue capable of harboring the streptococcus and other organisms, it leaves behind large areas of lymphoid tissue easily capable of becoming infected. The effect of tonsillectomy on the subsequent development of sore throats may be evaluated in two ways: first, by recording the incidence of sore throats over a period of years in tonsillectomized and in non-tonsillectomized persons; second, by observing the incidence of sore throats during a single outbreak of streptococcal disease.

It must be emphasized in this discussion of the role of tonsillectomy in patients with sore throats that bacteriologic and serologic studies have seldom been reported. This becomes more significant in the light of recent studies which have shown that in a large percentage of patients with acute sore throat during non-epidemic times the streptococcus cannot be incriminated as the etiologic agent.⁵

Paton observed a group of 909 girls attending a boarding school in England between the years of 1930 and 1939.¹⁶ Histories were taken of previous health and records were kept of illnesses while in the school. Fifty-seven per cent of the girls had had tonsillectomy prior to admission. Of interest is the fact that remnants of tonsillar tissue were present in 40 per cent of this group. This, however, represents the results to be expected in the usual tonsillectomy. The incidence of "follicular or lacunar tonsillitis" was about five times as great among those in whom no operation had

been performed as in the tonsillectomized group.

The following figures, taken from Paton and calculated on admission rate per 100 girls, were broken down further as to whether or not adenoids as well as tonsils had been removed.

	Operation			No Operation
	Tonsils and Adenoids	Tonsils Only	Adenoids Only	
No. of girls	435	57	24	393
Pharyngitis (%)	40	53	54	41
Tonsillitis (%)	1	2	4	5

"The reduction in tonsillitis after tonsillectomy . . . was not, that is to say, accompanied by a corresponding increase in sore throat from other causes; it was a true reduction." Paton stresses that too much reliance must not be placed on percentages calculated from such small numbers. The important feature was, however, that the incidence of pharyngitis in the two groups was the same. Cultural studies were not reported in this survey.

Kaiser's study of 4,400 children in Rochester, New York, has provided many interesting data.¹³ At least two febrile attacks of tonsillitis occurred during the first seven years of life in approximately 38 per cent of the 4,400 children. Tonsillectomy for one indication or another was advised for the entire group but for various reasons was performed in only 2,200. The incidence of previous sore throats was not significantly different in the two groups. At intervals of one, three and ten years after operation had been advised, the patients were re-examined and their parents were interviewed as to illnesses of the children in the intervening years. This study is open to criticism on several grounds. Parents whose children have had tonsillectomy are likely to emphasize their good health after operation. Furthermore, anamnestic histories are necessarily fraught with error. Never-

theless it is interesting to compare the figures for the two groups. In the first three-year period following operation sore throats occurred in 36 per cent of the non-operated group as compared with 3 per cent of the operated group.

At the ten-year follow-up 10 per cent of the operated group had had sore throats as compared with 35 per cent of the non-operated group. Kaiser correctly emphasizes that even in the absence of tonsils, sore throats involving the pillars and pharynx may still occur and cause illness as severe and as detrimental to the health of the child as that caused by acute tonsillitis. Nevertheless, his study provides evidence that in patients subject to repeated severe sore throats, tonsillectomy may diminish the likelihood of further attacks of sore throat.

Studies of population groups living under similar conditions and having comparable exposure to throat infections have brought out many interesting points. The Commission on Acute Respiratory Diseases reported detailed observations on an outbreak of type 5 beta hemolytic streptococcus tonsillitis and pharyngitis presumably caused by eating infected eggs.⁶ In the group studied tonsils were present in fifty-eight, tonsillar remnants (tags) in twenty-three and complete absence of tonsillar tissue in six. No mention is made, however, of the incidence of tonsils in the exposed but non-infected group. In patients whose tonsils were absent the disease was not modified to an important degree as compared with those whose tonsils were present. However, in the group with tonsils a predominant growth of streptococci was found more frequently than in the tonsillectomized group. Also, exudate was more abundant in patients with tonsils. Furthermore, at the end of six weeks 50 per cent of the individuals with tonsils still had positive throat cultures whereas only 20 per cent of the tonsillectomized persons had positive cultures. The difference is statistically significant.

Rantz, Spink and Boisvert have made a careful study of a food-borne throat infection in a military hospital group. The

causative organism was type 1 beta hemolytic streptococcus.¹⁸ Fifty-eight patients, all equally exposed to the offending food, were selected for further investigation. Sixty per cent of these became infected, as judged by cultural and serologic studies. It was not possible to determine all factors preventing infection in the other 40 per cent but a striking factor was the presence of tonsils in 48 per cent of the non-infected as compared to 94.3 per cent of the infected group. They contrasted this observation with those made in another large group of cases in which infection by a variety of types of hemolytic streptococci occurred. In this study the absence of tonsils did not interfere with the development of streptococcal sore throat. Tonsillectomy had been performed in 33 per cent of the group suffering from streptococcal infections and in 34.4 per cent of the group with non-streptococcal throat infections.¹⁹

Bloomfield studied a group of nurses during the course of a year.² In this period of time streptococcal tonsillitis occurred in 8 per cent of those tonsillectomized and in 30 per cent of those not having had a tonsillectomy. He concluded that in the group under study the absence of tonsils did offer considerable protection against infection with the hemolytic streptococcus.

A large group of patients diagnosed as having endemic pharyngitis was observed by the Acute Respiratory Disease Commission.^{8*} These patients primarily were recent inductees in a large Army training center. In those patients with exudative pharyngitis the frequency of positive culture for hemolytic streptococci and the antibody response was the same irrespective of the

* In passing it should be pointed out that these workers have demonstrated that in the patients with exudative pharyngitis, in non-epidemic times, beta hemolytic streptococci are isolated (in predominant numbers) in 50 per cent of the patients, and that in only 50 per cent of those with beta hemolytic streptococci is an antibody rise indicative of streptococcal infection demonstrated. De Wesselow had arrived at similar conclusions in England in 1935 when he noted a heavy predominance of beta hemolytic streptococci in only 25 per cent of 354 patients with tonsillitis seen in the clinic over a period of one year.⁷

presence or absence of tonsillar tissue. Rantz, Spink and Boisvert, as mentioned previously, have pointed out that tonsillar tissue seems to play no appreciable role in the development of throat infection with the hemolytic streptococcus except in explosive outbreaks due to one specific type.¹⁸

Although the evidence is not complete and is at times conflicting, the data at hand would seem to suggest the following. The frequency of sore throats appears to be reduced in those individuals whose tonsils have been removed. In outbreaks of streptococcal disease caused by a single type of the organism, tonsillectomized individuals similarly appear to be protected to some extent. When infection is caused by more than one type of the streptococcus, tonsillectomized individuals apparently are not spared to any significant degree. It must be emphasized, however, that most reports have not included bacteriologic studies. This becomes even more important when it is realized that endemic pharyngitis in a large percentage of cases is not caused by the hemolytic streptococcus.

Most authorities advise tonsillectomy in patients subjected to repeated severe sore throats, by which is meant one or more attacks a year. It is to be re-emphasized, however, that this does not insure against reinfection of the pharynx by the hemolytic streptococcus or by other pathogens.

RHEUMATIC FEVER

The concept that rheumatic fever represents an abnormal response to a streptococcal infection, particularly of the pharynx, has been accepted by most writers.²⁵ Many workers have shown that a rise in anti-streptolysin titer, signifying infection by the beta hemolytic streptococcus, occurs in nearly all patients with acute rheumatic fever. Rantz, Boisvert and Spink in recent war experience with group A beta hemolytic streptococcal disease have re-emphasized the rôle of this organism in the pathogenesis of rheumatic fever.¹⁷

Granted that acute rheumatic fever is

preceded by infection with the streptococcus in most, if not all, instances, it is natural to inquire whether removal of a large focus favorable for growth of the organism, namely, the tonsils, will prevent the development or alter the subsequent course of the disease. In an attempt to answer such questions one is forced to rely on statistical reports of large groups, despite the fact that there are many sources of error in the collection of such data.

Kaiser's previously mentioned study is of interest.¹³ Before tonsillectomy the incidence of chorea, rheumatic fever, muscular pains and rheumatic carditis was the same in both groups. The two groups were of comparable ages. After operation the figures were as follows: Chorea: operated group, 1.1 per cent, control, 0.6 per cent; rheumatic fever: operated, 2.3 per cent, control, 3.5 per cent; muscular pains: operated, 7.8 per cent, control, 9 per cent; rheumatic carditis: operated, 1.1 per cent, control, 1.3 per cent. None of these differences appears to be significant.

In another study Kaiser analyzed the records of 48,000 children, histories having been obtained from the parents.¹² Twenty-eight thousand of this group had had tonsillectomy, and among these there were 339 cases of rheumatic fever (1.9 per cent) as compared to 876 cases (3.0 per cent) in the unoperated group. Growing pains, chorea and rheumatic carditis were of similar incidence. He points out that children without tonsils do not escape rheumatic fever in sufficient numbers to justify the procedure of universal tonsillectomy as a preventive measure.

Similar observations have been recorded by other investigators. Wallace and Smith studied the records of children in Edinburgh.²⁶ They divided their patients into two groups: Group I comprised 403 children whose tonsils had been removed before the age of five and who had not had rheumatic fever. Group II comprised 574 children whose tonsils were removed in later childhood. Before "school leaving age" acute rheumatism, i.e., chorea, rheumatic fever

and carditis, had occurred in 7.2 per cent of the first group as compared with 4.2 per cent of the second group. There was a higher percentage of males in the first group which, they believe, should if anything make the incidence of rheumatic fever lower. They concluded that the procedure fails completely to protect a child against rheumatic fever and that it may even render him more liable to develop the disease. It should be pointed out, however, that in a group of children under five whose tonsils are removed there is apt to have been more preceding streptococcal disease. The study of Campbell and Warner is similar.³ Of 124 children with "complete removal of tonsils" 15.3 per cent subsequently developed rheumatic fever. There were 843 who never had tonsillectomy and 18.6 per cent of these developed rheumatic fever.

It would appear from the above recorded surveys that the operation of tonsillectomy will not offer protection against the development of rheumatic fever, hence the procedure should not be offered as a universal prophylactic. This seems logical for although tonsillectomy will remove a large body of tissue that is capable of harboring streptococci, nevertheless considerable amounts of lymphoid tissue are left in the nasopharynx even after the cleanest of tonsillar and adenoid enucleations. Moreover, rheumatic fever may be precipitated by a transient and superficial infection of the pharynx by the streptococcus.

Effect of Tonsillectomy on Recurrences. Hunt and Osman⁸ were among the first to question the efficacy of tonsillectomy in the management of the patient with rheumatic fever. They conducted follow-up studies on 144 rheumatic fever patients, of whom sixty-six had had tonsillectomy and seventy-eight had not. Recurrences were noted in 53 per cent of the operated group as compared with 42 per cent in the control group. Further analysis of these data in relation to recurrences after a first and second attack revealed a similar situation. These workers concluded that tonsillectomy was not a

certain protection against recurrences, and that, if anything, it was inducive of a higher recurrence rate. Kaiser makes the unqualified statement that recurrent attacks of rheumatic fever are as likely to occur in children whose tonsils have been removed as in those in whom they are still present.¹³ In his group of 439 children observed for five years those who had developed the first attack of rheumatic fever before tonsillectomy had a recurrence rate of 28 per cent as compared with 27 per cent for the group whose first attack developed after tonsillectomy. This opinion is also held by Stokes,²⁴ Janeway¹¹ and Rantz.²⁰ Spink has the impression that the removal of tonsils does decrease the incidence of subsequent attacks of rheumatic fever although he states that for this view he has no statistical data.²³ If a patient with a history of rheumatic fever has repeated attacks of acute tonsillitis, he should have a tonsillectomy during an inactive phase of his disease in the hope of decreasing the incidence of sore throats. The chances are that it will not lessen the likelihood of recurrence of rheumatic fever.

Tonsillectomy in Relation to the Late Effects of Rheumatic Fever. The proper evaluation of this aspect of the problem is made difficult because of the extreme variability in the clinical course of rheumatic fever. Carditis with its subsequent valvular and myocardial scarring is the most serious of the sequelae of rheumatic fever. If it could be shown that tonsillectomy diminishes the incidence of carditis, the procedure would be not only advisable but imperative in the management of rheumatic fever. Such, however, does not appear to be the case.

The outcome of a group of 597 children who developed their first attack of rheumatic fever between the ages of five and ten years and who were followed for a period of ten years is presented by Kaiser.¹³ These patients were divided into three groups: (1) those whose tonsils remained in during the entire period of observation; (2) those whose tonsils were removed after the first attack; and (3) those whose tonsils were

removed prior to the first attack. The outcome of these groups is as follows:

Group	No.	Died, Per Cent	Recurred, Per Cent
1	156	13	46
2	254	4	44
3	187	7	48

The incidence of carditis was the same in the groups, but it was the author's impression that fatal carditis was less frequently noted in the tonsillectomized group. The figures of Allen and Baylor¹ tend to corroborate this.

Among other studies of interest is that of Campbell and Warner³ who noted that the incidence of carditis was not influenced by the presence of tonsils.

It would appear that tonsillectomy should be performed in patients with rheumatic fever for the same reason as in non-rheumatic subjects, namely, in an attempt to prevent frequent attacks of tonsillitis. It is the general belief, however, that the procedure should not be performed during the active stage of the disease. No sound evidence is available which would indicate that the procedure will lessen the patient's chance of recurrence or that it will appreciably alter the late effects of the disease.

GLOMERULONEPHRITIS

Most authors agree that acute glomerulonephritis is preceded most frequently by infection with group A beta hemolytic streptococcus.¹⁵ In the majority of instances the primary streptococcal infection is in the nasopharynx. Unlike acute rheumatic fever, however, nephritis may also follow streptococcal skin infections. Recurrences of glomerulonephritis are similarly preceded by streptococcal pharyngeal infections in most instances. The problem of the role of tonsillectomy in the management of glomerulonephritis is essentially the same as that in rheumatic fever, i.e., does the operation prevent the disease, modify its course or prevent recurrences.

Turning again to the work of Kaiser,¹² one finds the statement that the absence of tonsils gives the child only a slightly better chance of escaping glomerulonephritis. Illingworth observed 365 patients with glomerulonephritis at the Great Ormond Street Hospital for sick children.⁹ Three hundred one of these patients were in the acute stage. Twenty per cent of the children had had tonsillectomy before admission in their acute episode as compared with an overall incidence for tonsillectomy of 9 per cent in the general population of comparable age groups. He believed that the procedure not only did not prevent the disease but that in several instances it actually precipitated an episode of acute glomerulonephritis. The factual evidence for the latter statement is, however, rather meager.

In considering the effect of tonsillectomy on the course of glomerulonephritis one finds the same paucity of facts on the ultimate outcome of the disease as were found in the study of rheumatic fever. One of the most comprehensive studies of acute glomerulonephritis is that recently reported from Sweden by Rudebeck.²² He has followed 318 patients with acute and subacute glomerulonephritis over a period of twenty-three years. In this group 69 per cent were listed as recovered, 19 per cent as uncertain and 11 per cent as not recovered. In the period from 1923 to 1933 tonsillectomies were done early in the disease. This apparently had no effect on the ultimate outcome of the disease, for of the fifty-two tonsillectomized patients 67.3 per cent recovered, in 21.2 per cent the outcome was uncertain and 11.5 per cent did not recover. Of sixty-three patients not operated upon 69.8 per cent recovered, the outcome was uncertain in 19.0 per cent and 11.1 per cent did not recover. Similarly he was unable to detect any differences in the recurrence rate in the tonsillectomized and non-tonsillectomized group. Rudebeck concludes that those reports of apparent improvement in the course of the disease are not valid either because the controls were not adequate, because follow-up

studies were insufficient or because data were misinterpreted.

Illingworth's⁹ analysis of the outcome of the 301 patients with acute glomerulonephritis is shown in Table 1. He concludes that in no instance can it be said that tonsillectomy had any immediate beneficial

appear to be those for tonsillectomy in general, namely, for frequent episodes of acute tonsillitis.

COMMENT

It is not the purpose of this review to attempt to draw sweeping conclusions but

TABLE 1*
EFFECTS OF TONSILLECTOMY ON THE OUTCOME OF PATIENTS WITH GLOMERULONEPHRITIS

	Cases	Urine on Discharge			Died in Acute Stage	Subsequent History		Latent or Active	Re-examination 1 to 12 Years after Onset	
		Un-known	Ab-normal	Normal		Died	Exacer-bation		Doubt-ful	Healed
Tonsillectomy more than 6 months before onset of nephritis.....	61	28	28	5	0	2	0	15	3	3
Operation probably caused nephritis.....	15	7	8	0	0	0	0	4	0	0
Tonsillectomy performed as therapeutic measure within 6 months of onset.....	119	67	44	8	1	2	7	23	4	7
Control children in whom tonsillectomy was not performed.....	106	45	52	8	13†	0	4	20	4	3
Totals.....	301	147	132	21	14	4	11	62	11	13

* From Illingworth.⁹

† Most died in first few days of disease.

effect on the nephritis, nor that it had any effect on the subsequent course of the disease.

It would appear that tonsillectomy offers little in the management of the patient with glomerulonephritis. Certainly it will not prevent the disease and apparently it does not alter its course. There is fairly general agreement that tonsillectomy during the acute stage of glomerulonephritis is quite apt to provoke an exacerbation with an increase in the elements in the urinary sediment, a rising NPN and further elevation of blood pressure.¹⁴ In the quiescent or latent stage of glomerulonephritis the removal of tonsils in the hope of preventing recurrence of the disease or the likelihood of further renal damage lacks supportive evidence. In patients with glomerulonephritis the indications for tonsillectomy would

rather to present evidence on the question of the efficacy of tonsillectomy in the disease states discussed. The need for more carefully controlled studies with adequate bacteriologic and serologic data cannot be over-emphasized. Tonsillectomy is frequently recommended with claims that dramatic changes in health may ensue. No attempt has been made to go into the effect of the procedure on the growth, development and general health of the child. Tonsillectomy is not completely without risk. Rare though complications may be, they do include fatal hemorrhage and pulmonary abscess. Furthermore, evidence seems to indicate that the operation increases the likelihood of developing bulbar poliomyelitis during an epidemic period. Weighing all factors, it would seem that tonsillectomy, not a completely innocuous procedure, should not be

performed indiscriminately. Each individual case must be considered on its own merits.

CONCLUSIONS

Patients with repeated episodes of acute severe sore throats can be expected to have a decreased number of attacks after tonsillectomy. The available evidence does not indicate that tonsillectomy will prevent or will appreciably alter the course of acute rheumatic fever or of acute glomerulonephritis, or that it will diminish the incidence of recurrence of these diseases.

Further careful clinical, bacteriologic and immunologic studies on a large unselected group of people are needed before positive conclusions can be drawn.

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Seminars on Congestive Failure

Pathogenesis of Renal Dysfunction during Congestive Heart Failure*

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CONGESTIVE heart failure involves a complex of disorders affecting nearly every organ system of the body. No one denies that the cardiac lesion is of primary importance in initiating the chain of events that culminates in a rising venous pressure, accumulation of edema and evidences of renal dysfunction. There is sharp disagreement regarding the sequential position and the relative importance of these changes in connection with the cardiac disturbance. One important cause for dispute lies in the emphasis placed upon the role of the kidney in the formation of edema. On the one hand, an elevation of venous and capillary blood pressures is regarded as instrumental in diverting fluid from the vascular bed into the tissues and thus in provoking an over-active conservation of water and salt by the kidneys.^{1,2} On the other hand, abnormal renal retention of water and salt due to the "cardio-circulatory" imbalance is believed to result in an expansion of plasma volume and an increase in venous pressure with the coincidental development of edema.^{3,4} This paper is devoted to an analysis of renal abnormalities in congestive failure with the purpose of reconciling these opposing views.

EVIDENCE OF RENAL DYSFUNCTION DURING FAILURE

There is little anatomic evidence of renal damage in congestive heart failure.

The kidneys may be enlarged as a result of venous engorgement and dilatation of the peritubular capillaries.¹ The glomerular capillaries are rarely if ever involved. Occasionally cloudy swelling and fatty infiltration of tubular cells are found but as a rule the parenchyma is unaffected. In contrast, marked changes in the character of the urine occur. Proteinuria and cylindruria develop in the majority of patients and microscopic hematuria is occasionally encountered.^{5,6} The urea clearance and phenolsulfonphthalein excretion are usually depressed. It is particularly interesting that the urinary specific gravity tends to rise and to remain fixed at an unusually high level in many cases. This fact has been cited¹ as evidence of a fundamentally adequate renal function, other changes being incidental to the augmented activity of the kidney in conserving water and electrolytes. Perhaps the most striking and certainly the most important renal dysfunction is retention of water and sodium.

It has been recognized^{7,8} for many years that restriction of water and salt intake may control and even prevent edema. This phenomenon has been placed upon a quantitative basis only recently.^{9,10} The sodium ion appears to be selectively affected in failure since water loading alone is not uniformly followed by a gain in weight whereas increased sodium intake in association with adequate hydration results in

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striking edema formation. Other electrolytes are relatively undisturbed so that retention of sodium need not involve a linked retention of chloride. Although chloride does tend to follow sodium, the urinary sodium/chloride output ratio usually falls.¹¹ The kidneys fail to regulate the total body content of sodium and water normally but they usually continue to maintain the plasma composition within normal limits.¹² Occasionally marked azotemia with retention of all the components of the non-protein nitrogen is encountered and, rarely, the serum concentration of sodium and chloride may fall, apparently because of sodium restriction and failure to eliminate excess body water.²

RENAL HEMODYNAMIC ADJUSTMENTS DURING FAILURE

Recent investigations¹³⁻¹⁶ have sought to define the renal hemodynamic adjustments during congestive failure in relation to sodium and water excretion. A variable depression of renal blood flow and glomerular filtration rate has been found. In some individuals these values may be reduced to as low as one-third and one-half the normal values, respectively, when edema is present. There is a definite tendency to return toward the normal with compensation. Blood flow is always affected to a more marked degree than filtration and the percentage of plasma filtered at the glomerulus consequently increases. Since the change in blood flow occurs in the absence of a similar change in arterial pressure and since it is apparently independent of the level of renal venous pressure, decompensation must evoke a striking increase in renal vascular resistance. Most observers believe that both afferent and efferent arterioles are involved, because the glomerular filtration rate tends to fall and the filtration fraction rises. In this view, diminished filtration is a manifestation of diffuse intrarenal vasomotor activity which presumably affects each glomerulus to some extent. These data do not preclude the possibility that filtration is reduced because a certain proportion of

nephrons become completely inactive. In such a case the vasomotor activity might involve afferent arterioles almost exclusively or blood might perfuse non-functioning glomeruli, the behavior of the filtration fraction then having little meaning in terms of glomerular dynamics. Whatever its distribution, intrarenal vasoconstriction is characteristic of heart failure and it accounts in part if not entirely for the diminution of glomerular filtration.

The kidneys appear to operate in the systemic circulation as vascular buffers. Intrarenal vasoconstriction results in the diversion of a considerable quantity of blood to other tissues and thus serves to support arterial pressure and to supplement, in effect, the cardiac output.¹⁷ This response has been observed under many circumstances, e.g., in hypotensive states following blood loss, trauma and fever; on assumption of the upright position; during chronic anemia, in Addison's disease, exercise, fright and in anger; as well as following the injection of various pressor agents. These renal vascular responses differ mainly in the degree to which afferent arteriolar constriction occurs. Many conditions characterized by a reduction in *circulating* blood volume (shock, orthostasis, Addison's disease, chronic anemia) present evidence of preponderant afferent arteriolar constriction.¹⁸ This activity may so interfere with the nutrition of the kidney in shock that irreversible damage may ensue.¹⁹ It is true that abundant and apparently reliable evidence indicates a marked expansion of blood volume in congestive failure.²⁰ But a considerable portion of this volume is probably pooled in dilated veins of the dependent extremities, the abdomen and the abdominal viscera so that effective *circulating* blood volume is reduced. Measurements of this variable are not feasible at present and this possibility cannot be explored. In any event, the patient with failure behaves as if inadequate venous return and/or cardiac inefficiency interferes with normal circulatory regulation.

A reduction of cardiac output is demonstrable

in most patients with congestive failure at rest.^{21,22} A compensatory increment in total peripheral resistance is necessary to maintain arterial pressure within normal limits in these individuals and renal vasoconstriction out of proportion to that elsewhere in the body is not unexpected since this is a situation dynamically similar to shock. Myers²³ has found that excessive compensatory vasoconstriction also develops in the hepatoportal circuit, which is not surprising in view of the increasing evidence that this vascular bed is also important in circulatory adjustments. Excessive compensatory vasoconstriction in some individuals may elevate the arterial pressure well above normal values. In a small group of patients decompensation occurs in association with an augmented cardiac output,^{22,24-26} the so-called "high output failure" of cor pulmonale, arteriovenous fistula, thyrotoxicosis, Paget's disease, beriberi and chronic anemia. Obviously peripheral vascular resistance is much diminished in these cases but intrarenal vasoconstriction develops nonetheless.¹⁴ It may be surmised that this is a response to an instability of arterial pressure resulting from an inefficient maintenance of cardiac output. This assumption finds support in the fact that cardiac output tends to *fall* and pulmonary arterial pressure tends to rise during exercise in both types of failure, indicating outright or potential cardiocirculatory imbalance exaggerated or unmasked by stress. The disturbance in renal blood flow is also grossly exaggerated during exercise.^{29,30}

Little is known regarding the *mediation of vasoconstriction* in the kidney or in other parts of the body during failure. Starling³¹ suggested that a preliminary fall in arterial pressure might elicit such a response to return blood pressure to normal and thereby to assure continued perfusion of the brain. This view has much to recommend it since hypotension develops frequently and since the inadequate response of cardiac output during stress predisposes to a fall in arterial pressure. This stimulus might be expected to influence renal function by reflex action,

but recent work by Mokotoff and Ross³² suggests that renal vasoconstriction in failure does not require continuous activity of the autonomic nervous system. In their studies spinal anesthesia did not alter renal blood flow provided arterial pressure was maintained by ephedrine. However, ephedrine has been found to cause intrarenal vasoconstriction³³ and it is possible that the effect of spinal anesthesia may have been masked. Moreover, high spinal anesthesia does not alter the blood flow through the normal kidney during rest in recumbency³⁴ although it does alter profoundly the ability of the vascular system as a whole to adjust to changes of state. Elevation of the body after intrathecal administration of procaine is quickly followed by hypotension and syncope. Possibly autonomic reflexes are instrumental in establishing a given state of vascular tonus and in maintaining or altering it during stress as needs demand; whereas independent local mechanisms maintain the imposed tonic state during periods of little change. According to this point of view therefore the constancy of renal blood flow during spinal anesthesia does not exclude autonomic activity as an initiating cause of vasoconstriction during failure since the autonomic system is called upon to act only during stress. The role of hypothetical humoral agents in mediation of the vasoconstrictive response is difficult to evaluate. It has long been believed that hypertension during failure may arise from interference with renal blood flow and stimulation of renin formation. Merrill³⁵ has provided evidence for this view by finding an increased renin content of the renal venous blood in eight of eleven patients with chronic congestive failure who had no intrinsic renal disease. He does not state whether the blood pressure was elevated in these patients. Renin cannot be considered a cause of renal vasoconstriction since renal ischemia presumably must precede its production. No other humoral agents have been detected in congestive failure although it is not unlikely that certain internal secre-

tions may be active in promoting retention of salt and water.

There is little doubt that marked *renal anoxia* may develop in certain patients with congestive failure but it appears to be a late manifestation occurring long after edema formation has begun, having little significance in the development of the clinical syndrome of failure. Renal anoxia similar to that obtaining early in failure appears to enhance salt and water excretion. A marked polyuria develops soon after reduction in oxygen saturation of the blood by inhalation of oxygen-poor gas mixtures³⁶ and sodium, potassium and chloride excretion rises.³⁷ It seems quite unlikely therefore that the anoxia-producing effect of renal ischemia is implicated. The change in renal blood flow is probably significant in relation to sodium and water retention only insofar as it is associated with a depression in glomerular filtration.

GLOMERULAR FILTRATION AND TUBULAR REABSORPTION OF SODIUM AND WATER DURING FAILURE

Glomerular filtration is of crucial importance in this connection because it has been shown¹⁷ that water and the sodium and chloride ions are excreted by filtration alone. A very large volume of filtrate—in excess of 180 L.—is formed daily whereas only a small quantity of urine is eliminated, indicating tubular reabsorption of almost all the filtrate. Since such a small proportion of the filtrate is excreted, it has been customary to think of tubular activity as decisive in determining output. Water reabsorption occurs largely in the proximal segment where it apparently follows sodium reabsorption passively with maintenance of “iso-osmoticity” of urine in the proximal segment.^{38,39,40} Numerous studies^{41,42} have demonstrated that distal tubular water reabsorption is an active process, independent of sodium reabsorption, which is carried out under the influence of the neurohypophysis. This apparatus is said to be activated by “osmoreceptors”—located in the region supplied by the external carotid.⁴³ The

osmoreceptors respond to changes in plasma osmotic pressure, especially when due to changes in the concentration of plasma sodium. Sodium excretion, on the other hand, may be controlled by minute fluctuations in filtration.⁴⁰ The usual range of excretion (20 to 160 mEq./day) under normal circumstances represents only from 0.01 to 0.1 per cent of the total filtered sodium. It has been postulated^{40,44} that a constant absolute quantity or proportion of most of the filtered sodium is reabsorbed in the proximal segment and that a limited transfer mechanism in the distal segment controls output in association with changes in filtration; increased filtration serving to increase slightly the distal tubular loading of sodium beyond the capacity of the transfer mechanism so that increased excretion occurs, whereas decreased filtration reduces the load below the transfer capacity and permits reabsorption of almost all filtered sodium. Unfortunately, the changes in filtration necessary to such a mechanism are too small to be detected by methods at present available and the hypothesis cannot be tested critically.

In conformity with this view, Mokotoff, Ross and Leiter¹⁵ have found that the proportion of sodium reabsorbed remains unchanged within narrow limits in both normal and decompensated patients. Since filtration is usually somewhat reduced and *total* sodium reabsorption depressed, they conclude that sodium retention in heart failure is a result of the decreased filtration rather than increased tubular reabsorption of sodium. The quantities involved in these calculations differ so greatly in magnitude that the mathematic manipulations and correlations may be very misleading. The quantity of sodium excreted per minute under all circumstances is negligibly small and in consequence an excellent correlation between filtered load and sodium reabsorption is inevitable over a wide range. In the published data,¹⁵ however, a departure from the predicted relation is evident at high plasma levels of sodium even though filtration has increased, de-

noting the intervention of a change in tubular reabsorption as a factor of importance. In evaluating the reduction in *total* sodium reabsorption it must be remembered that such a reduction does not preclude increased reabsorptive activity by a smaller

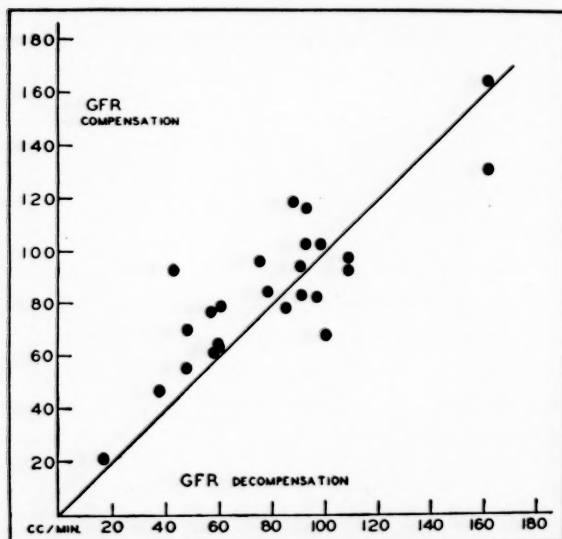


FIG. 1. Change in glomerular filtration rate during recovery from congestive heart failure. Values for glomerular filtration rate (GFR) taken from Seymour et al.,¹³ Merrill,¹⁴ Mokotoff, Ross and Leiter¹⁵ and Briggs et al.¹⁶ during decompensation are plotted against values obtained in the same individuals after recovery. The points above the diagonal are from patients in whom filtration rose during compensation whereas those below the line denote a fall in filtration. Filtration was usually reduced in failure close to or below the lower limit of normal (about 90 cc. per minute). In many patients there was no significant change in filtration with recovery and in a few it fell.

number of functioning nephrons. Filtration may be diminished as a result of diffuse or focal glomerular involvement. Most writers have made the tacit assumption that the lower filtration rate in failure arises from a decrease in filtration in all glomeruli and that the filtered load of sodium and water imposed upon the tubules therefore is greatly reduced. It is equally possible that filtration has ceased altogether in some glomeruli, filtration in the remainder being somewhat reduced, remaining unchanged or even increasing, depending upon the number of inactive nephrons. There is no evidence available in the literature to provide an answer to this question, but un-

published work by Earle⁴⁵ and Leiter⁴⁶ has disclosed a significant fall in the transfer maxima of sodium *p*-aminohippurate (PAH Tm). It seems likely therefore that the glomerulotubular imbalance is not as great as it appears to be in many patients and that reabsorption may be relatively increased.

Certain additional considerations are opposed to the view that deficient filtration alone accounts for sodium retention. In Figure 1 data from the literature¹³⁻¹⁶ for filtration rate during and after recovery from congestive failure are plotted. Filtration rate fell within normal limits (lower limit about 90 cc. per min.⁴⁷) in a significant proportion. Unquestionably, the values were low normal or abnormally low in the majority but this change appears to have had no clear-cut relationship to the degree of water and salt retention evident as edema in these individuals. Of even greater importance is the observation that filtration showed no consistent change during return to compensation. Very small increments may have served in some instances to promote diuresis and mobilization of edema but in at least seven patients filtration fell during compensation without in any way preventing the diuretic response to therapy. Salt and water diuresis has also been observed acutely following intravenous injection of digoxin in decompensated patients before any change took place in glomerular filtration or renal blood flow.⁴⁵ Finally, filtration may be much more markedly disturbed than it is in most recorded instances of heart failure without evidence of edema formation. This is particularly true when filtration is disturbed by intrinsic renal disease such as nephrosclerosis, without a corresponding alteration in tubular function.⁴⁸ These patients often display a remarkable ability to regulate sodium and water balance and they may live for years with filtration rates as low as any of those recorded in congestive failure, responding to excesses or deficits of salt and water with normally appropriate although often less exact and speedy adjustments. In chronic

anemia edema formation is occasionally seen.⁴⁹ It is prone to occur in pernicious anemia during return of the hematologic picture to normal. The renal blood flow has been found to be greatly reduced in this condition though glomerular filtration is not much affected.¹⁸ The intrarenal vasoconstriction appears to be but slowly reversible and in consequence a rise in hematocrit in response to therapy may lead to replacement of plasma by red cells in the unchanging volume of blood perfusing the kidney. The renal plasma flow and filtration rate may then fall as in the patient whose course is plotted in Figure 2. Edema formation under these circumstances may be attributed to the fall in filtration since glucose T_m is demonstrably normal and definite increase in glomerulotubular imbalance must develop. In the subject illustrated in Figure 2, however, edema did not appear. There was a slight gain of weight which persisted after complete recovery, probably as a result of improved appetite and diet. It is of great interest that in this patient and in one other¹⁸ edema did not form despite the fall in filtration and an unchanged (or augmented) intake of salt and water. It may be concluded therefore that an alteration in glomerular filtration of a degree similar to that usually observed in congestive failure is usually insufficient in itself to induce water and salt retention with edema formation. Although it should be emphasized that the change in filtration probably contributed importantly and may provide a necessary setting for this development, other factors must be implicated. Among these a relative augmentation of sodium reabsorption may play a role.

Tubular reabsorption of sodium is so large that small and scarcely detectable changes will produce large changes in the urinary output of sodium. It is an active process affected by the concentration gradient between blood and urine, by the presence of osmotically active materials in the filtrate and by various humoral agents.^{40,50} None of these factors is known to operate in failure although it has been

suggested^{51,52} that overproduction of anti-diuretic hormone by the posterior pituitary may occur. Recent work indicates that tubular reabsorption of water and salt is increased by elevation of the renal venous pressure. Since venous hypertension is

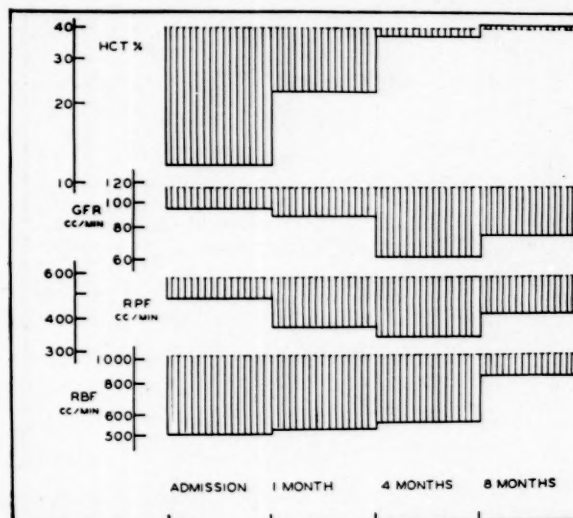


FIG. 2. Change in renal function during treatment of pernicious anemia. In E. M., a fifty-seven year old white female with pernicious anemia of about six months' duration, treatment with liver extract resulted in a return of the hematocrit (HCT) from 12 per cent to normal within four months. The reduction in renal blood flow (RBF) persisted for four months and may be attributed to intrarenal vasoconstriction which was slowly reversible. With improvement the glomerular filtration rate (GFR) and renal plasma flow (RPF), measured by the mannitol and sodium *p*-amino-hippurate clearances, respectively, fell from values somewhat lower than average normal (baselines) to abnormally low levels, apparently as a result of replacement of plasma by red cells with the rise in hematocrit. Despite the marked change in filtration in this patient there was no evidence of edema formation.¹⁸

prominent in failure, this response is undoubtedly of importance.

EFFECT OF ELEVATED RENAL VENOUS PRESSURE ON SODIUM AND WATER EXCRETION

It has been known for many years that obstruction to the venous outflow of the isolated kidney results in diminished output of salt and water,⁵³ but owing to the uncertainties and inaccuracies inherent in the heart-lung-kidney preparation clinicians have been reluctant to accept the implications of these observations. Renal

function studies in man have revealed a depression in sodium and water excretion when intra-abdominal venous pressure is raised to 20 mm. Hg by external abdominal compression with a pneumatic girdle.⁵⁴ Glomerular filtration and renal blood flow

blood flow, filtration rate and tubular activity apparently change chiefly as a result of the obstruction to urine outflow from a proportional number of nephrons. Subsequent work⁵⁵ has shown that the decrement in water output is associated

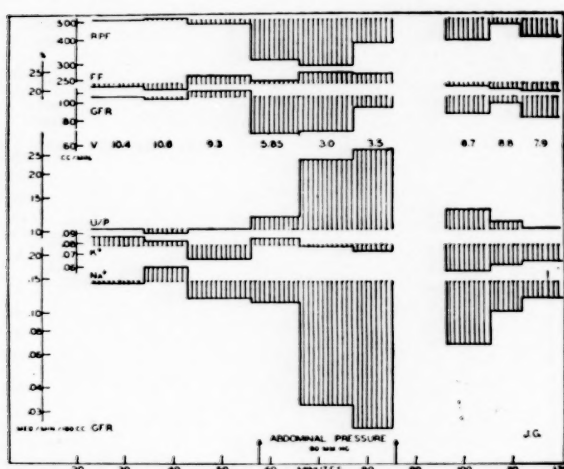


FIG. 3. Change in renal function during abdominal compression. J. G., a thirty-five year old white male with diabetes insipidus, was studied after re-establishment of diuresis on withdrawal of therapy. Clearance measurements of renal plasma flow (RPF), filtration fraction (FF), glomerular filtration rate (GFR), urine flow (V), and potassium (K^+) and sodium (Na^+) output were made before, during and after compression of the abdomen (between arrows) with a pneumatic belt under 80 mm. Hg pressure. Glomerular filtration rate and renal plasma flow decreased proportionately during compression of the abdomen so that the filtration fraction did not change. Urine flow fell greatly and mannitol concentration (expressed here as the ratio between urine and plasma concentrations (U/P)) increased, denoting increased water reabsorption relative to filtration. Sodium output expressed in terms of filtration rate ($\times 100$) fell off, but potassium output expressed in the same way did not change significantly. All values tended to return toward the average control values (baselines) after release of pressure. Similar results were obtained in studies of four other patients with diabetes insipidus and four normal subjects (from data of Mudge et al.⁵⁵).

are equally reduced in association with a proportionate reduction in active tubular mass as measured by diodrast and glucose Tm. Since all these values fall to approximately the same extent, there is no obvious glomerulotubular imbalance. Abdominal compression raises pressure in the renal pelvis as well as in the renal veins; and since the increment in venous pressure is sufficient to account for the reduction in

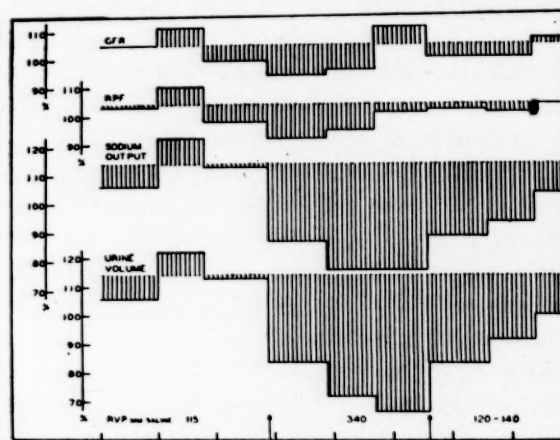


FIG. 4. Change in renal function in the dog during elevation of renal venous pressure. Values for glomerular filtration rate (GFR), renal plasma flow (RPF), urine flow and sodium output (mEq. per minute) of the left kidney are expressed here as percentages of the same functions determined simultaneously in the right or control kidney. During the control periods the left kidney put out 6 to 23 per cent more urine and sodium than the right, but with partial occlusion of the left renal vein and elevation of the left renal venous pressure from 115 mm. saline to 340 mm. saline (between arrows) there was a striking decrease in these values on the left over the right. During this period filtration and plasma flow did not change from the average control values (baselines) more than expected on the basis of spontaneous fluctuations. Sodium and water output of the two kidneys approached equality after the venous obstruction was removed (from data of Blake et al.⁵⁶).

with an even greater diminution in sodium excretion. The same response (Fig. 3) has been observed in five patients with diabetes insipidus following withdrawal of hormone therapy, indicating a direct effect upon the kidney rather than stimulation of the neurohypophysis. In all these studies the effect of obstruction due to elevated renal pelvic pressure cannot be separated from that of increased renal venous pressure.

Blake, Wégria, Keating and Ward⁵⁶ have investigated sodium and water excretion relative to glomerular filtration in the separate kidneys of dogs during unilateral elevation of renal venous pressure by partial

occlusion of one renal vein. Since renal function and urine flow change significantly only in the kidney subjected to increased venous pressure, humoral and neural activity appear to be unimportant. Sodium and water excretion are depressed when venous pressure exceeds 150 mm. saline with more and more depression at progressively higher levels. These changes occur without any clear-cut change in filtration and renal blood flow up to pressures of 400 mm. saline. (Fig. 4.) Filtration actually increased slightly on several occasions, definitely indicating enhanced tubular reabsorption. Renal blood flow did not decrease until venous pressure exceeded 400 mm. saline so that renal vascular resistance must have decreased in proportion to rise in venous pressure. Since filtration did not change, the resistance was probably lowered by passive distention of the renal veins, venules and peritubular capillary net. Such renal engorgement must be attended by an increment in renal interstitial pressure approximately equal to that in venous pressure and it may be supposed that engorgement influences water and sodium reabsorption by altering the gradient of pressure and flow of urine along the tubules—or possibly by changing the rate at which blood perfuses any given renal unit. These factors may also operate in conjunction with the vasoconstriction elicited by the erect position in causing the antidiuresis and lessened sodium output of orthostasis.^{57,58} Certainly elevated renal venous pressure within a range comparable to that observed during failure may adversely affect renal excretion of water and salt independently of humoral and vasomotor adjustments.

VENOUS DYNAMICS DURING FAILURE

The pressure in renal veins and elsewhere in the venous system derives from the complex interaction of the residual arterial pressure, the volume of blood held in the veins, the rate of blood flow into and out of the venous chambers, tissue tension and the "tonus" of the venous system as a whole.

In addition, skeletal muscular activity imposes further pressure changes and drives blood "uni-directionally" through valved vessels. Dynamically, the central venous reservoir is divided into two major compartments in which pressures may vary more or less independently.^{59,60} The pressure rises during expiration in the superior caval system (the supracardiac chamber) and falls in the inferior caval system (the subcardiac chamber). During inspiration the changes are reversed. Blood flows in opposite directions in these chambers under pressure gradients which are unrelated except that both are centered upon the right atrium. This independence is seen more strikingly during assumption of the upright position when pressure rises throughout the subcardiac chamber and falls almost to atmospheric pressure in the supracardiac chamber. The behavior of the total venous system cannot be characterized on the basis of pressures measured in a single peripheral vein.

In frank congestive heart failure all the veins are greatly engorged with blood and venous pressures are elevated throughout. The pressure in the right atrium may increase more than in the peripheral veins with a reduction in the pressure gradient.⁶¹ This phenomenon as well as the obvious fact of cardiac disease in the vast majority of cases implicates defective cardiac function as an essential element in the production of venous hypertension. But other factors including increased venomotor activity, redistribution of blood, venous compression and increased blood volume must be involved.

According to Starr and his co-workers⁶² the right heart may be severely damaged in experimental animals without altering venous pressure. Warren and Stead³ claim that an initial expansion in blood volume is necessary. In careful studies of the clinical course of patients with heart disease they have observed that a notable gain in weight may precede any detectable change in venous pressure. The validity of this observation depends upon isolated measure-

ments of pressures at rest in peripheral veins. In view of the complexity of venous dynamics such measurements appear to be inadequate. Moreover central and peripheral venous pressures rise sharply in patients with cardiac insufficiency and in animals with heart damage during exercise whereas little or no change occurs in the normal.^{63,64,65} In man increments in renal venous pressure observed during exertion in recumbency are further augmented on standing by the superimposed hydrostatic column of blood. Under these circumstances there is a striking decrease in water and sodium excretion.^{29,30} Hence abnormal elevations of pressure which are not detectable at rest may occur frequently during the course of each day and may be expected to have a profound effect upon not only the transcapillary balance of forces but also upon renal function. In addition, recent studies by Roos and Smith⁶⁶ indicate that venous pressure may rise in dogs immediately after myocardial injury, provided damage is sufficiently extensive and diffuse. The causes of immediate elevation in pressure are obscure and need not concern us here. It is sufficient to note that the elevation in venous pressure probably precedes edema formation and contributes to the pathogenesis of renal dysfunction.

Hypervolemia is probably important in accelerating the development of failure. In experiments of Landis⁶⁴ and of Roos and Smith⁶⁶ on animals with cardiac incompetence, intravenous injection of a small volume of saline solution or blood hastened and accentuated the change in venous pressure. Likewise, incautious administration of fluids intravenously to patients with cardiac disease will often precipitate decompensation.⁶⁷ Hence renal retention of salt and water is undoubtedly detrimental. It is not surprising that therapy designed to induce diuresis and to reduce blood volume is helpful. On the other hand, numerous studies^{64,68,69} in man and animals indicate that expansion of the blood volume within wide limits will not induce a persistent elevation in venous pressure unless there is

pre-existing cardiac disturbance. The development of congestive failure is to be regarded therefore as presumptive evidence of cardiac incompetence, even though anatomic evidence of a disorder of the heart may be lacking.

CONCLUDING REMARKS

On the basis of these considerations it is possible to set out an hypothesis which provides a reasonable explanation for renal dysfunction in heart failure. The place of the heart in this process scarcely needs reaffirmation and re-emphasis. Ample evidence is now at hand to support the view that cardiac output is insufficient for normal circulatory adjustments. The vasoconstrictive response to remedy this affects particularly the renal vascular bed even when blood flow to other tissues is increased, as in anemia. In consequence of the intrarenal vasoconstriction, renal blood flow and glomerular filtration rate are reduced with resultant impairment of kidney function. Remittent or persistent elevation of renal venous pressure also develops and acts to enhance tubular reabsorption of salt and water. Thus two changes, renal venous hypertension and intrarenal arteriolar constriction, operate simultaneously to produce retention of salt and water. It is quite likely that they contribute variously in different cases, but both appear to be necessary. This belief finds strong support in the fact that left ventricular failure may develop and persist in the absence of edema formation as long as venous pressure does not rise.

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Combined Staff Clinics

Ulcerative Colitis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. DANA W. ATCHLEY: The natural history of ulcerative colitis is so variable that it would be proper to question the validity of its existence as a single disease. However, the different patterns of pathology and course present sufficiently similar etiologic and therapeutic problems to justify their classification as a single entity. Moreover, the complications of all types have common features that support this unitary approach.

The gross pathology of this disease is less consistent than the microscopic picture. Any part of the colon may be involved in all degrees of severity; the ileum may participate; abscesses may form; and polyposis is a late feature of serious significance. The clinical picture is equally diverse. Some patients are extremely ill with high fever and great prostration; pain or bleeding may be intense or completely absent. Unpredictable remissions and relapses make the evaluation of therapy most uncertain.

The most satisfactory approach to the analysis of a disease is afforded by the presence of a specific etiologic agent. Amebiasis presents such a situation. The topic of this clinic is not in that pleasant category. No hypotheses as to etiology have stood the test of critical study. Felsen has written extensively incriminating the dysentery group of bacilli, arguing that most patients with ulcerative colitis have either a history of bacillary dysentery or are carriers of the organisms. The majority opinion disagrees with Felsen. Dysentery bacilli are found in only a small percentage of cases and treatment of this disease with chemotherapy found effective in true bacillary dysentery is without benefit.

Bargen of the Mayo Clinic isolated a diplococcus in ulcerative colitis but his work has been discarded by most workers in this field. As in every obscure condition, allergy has its proponents but again no consistent evidence as to its etiologic role has been collected.

When the etiology of a disease remains obscure, a clear understanding of its mechanism may be an excellent substitute. The etiology of constrictive pericarditis is rarely assured but the dynamics of its effects on the circulation are so clear that therapy can be intelligently planned. Once again we find a relatively barren field in ulcerative colitis. The reason for the remissions and for the variations in pathology are equally obscure. However, recent biochemical studies may offer a clue to one of the factors in the production of this disease. Dr. Meyer will discuss the general subject of the lysozymes and then Dr. Prudden will tell us of the application of this knowledge to ulcerative colitis.

DR. KARL MEYER: The word "lysozyme" was coined by Fleming in 1918. He lumped together under this name a variety of agents found very widely distributed in nature which lysed not only certain air-borne organisms such as sarcinae and some micrococci but also certain micro-organisms shown subsequently not to be affected by lysozyme but presumably by other enzymes.

Lysozyme, as isolated from egg-white, one of the richest sources of this enzyme, is a basic protein of low molecular weight. It was crystallized a few years ago by Alderton and his co-workers who showed the molecular weight to be 18,500 and the isoelectric

point to be at pH 10 to 10.5. Mammalian lysozyme is quite similar and is the most basic protein found in warm blooded animals thus far. However, this basic property is not essential to the lysozymes in general. There are acidic lysozymes which occur in the latex of a wide variety of plants but they have the same specificity as the basic lysozymes of egg-white, of tears and of the gastric mucosa or of stool with regard to both their action on micro-organisms and their chemical specificities. Lysozyme acts on susceptible organisms by destroying (through hydrolysis) a constituent, a mucopolysaccharide, of the bacterial cell wall. The cell thus acted upon autolyzes, leaving behind an empty shell, a picture which is familiar from electron microscope studies of the action of bacteriophage.

A few years ago we obtained this substrate in a highly viscous form from *Micrococcus lysodeikticus*, a sarcina and an air-borne staphylococcus, which also happen to be susceptible to lysozyme. This viscous mucopolysaccharide is composed of an acetylated amino sugar and a phosphorylated polyhydric alcohol, which means that this polysaccharide belongs to the class of mucic acid polysaccharides. Lysozyme lowers the viscosity of solutions of this polysaccharide by hydrolyzing the glucosidic linkage of the hexosamine. In our method the loss of viscosity is measured, and we define as one unit the amount of lysozyme which produces half viscosity in ten minutes under standard conditions.

Crystalline egg-white lysozyme contains approximately 1,300 of such units per mg. Human tears contain about 1,400 units, but the tear glands of domestic animals and laboratory animals have a very low lysozyme titer. It is not known whether this high lysozyme titer in the tears or tear gland is characteristic for man or not, but it is very low in the animals which have been studied.

We studied further the distribution of lysozyme in the mammalian body and found rather surprisingly high concentrations in the gastric mucosa of man and some

animals. The pyloric region of man has a lysozyme titer of about 350 to 400 units per Gm. wet weight while serum has a titer of less than 1 unit per cc.

We then studied the action of lysozyme on the alimentary canal of experimental animals, which Dr. Prudden will discuss. These experiments have been confirmed and elaborated upon by two groups, one at Cornell Medical College working on ulcerative colitis, and one in Chicago working on the experimental effect of the action of lysozyme in animal stomachs. Contrary to our belief that lysozyme acts by depolymerizing an unknown constituent of the surface mucus, Dr. Grossman in Ivy's laboratory believes that lysozyme acts on the cells rather than on the surface mucus. We have not succeeded in isolating the substrate acted upon by lysozyme in the alimentary canal, which is a rather important and necessary step in the whole investigation. The known acid and neutral mucopolysaccharides of the gastric mucosa are not affected by lysozyme.

Lastly, I want to tell you about a few experiments on the inactivation of lysozyme. Lysozyme as it occurs in the alimentary canal and egg-white is a basic protein. We expected that acidic detergents would inactivate it and this proved to be the case. We chose the alkyl sulfates, half esters of sulfuric acid with a straight fatty alcohol chain, from C_{12} to C_{18} , for this study and found increasing inactivation of lysozyme as the carbon number increased. For example the C_{12} compound, dodecyl sulfate, inactivates 15 to 25 per cent of crystalline egg lysozyme in 5×10^{-3} molar solution while the C_{16} and C_{18} , the hexadecyl and octadecyl compounds, inactivate 82 per cent. The C_{16} compound has another advantage over the lower carbon member substances in that it does not react so readily with proteins less basic than lysozyme, particularly the serum proteins.

DR. JOHN F. PRUDDEN: Time does not permit presentation of the rather large amount of experimental work that has gone into the attempt to demonstrate that lysozyme is the local agent initiating the

lesions of chronic ulcerative colitis. We can summarize the work which has been done here by a team consisting of Dr. Karl Meyer, Dr. Alfred Gellhorn, Dr. William Lehman and myself¹ by saying: (1) Lysozyme can, when present in high concentration, remove the surface mucus of any portion of the alimentary tract from the cardia to the anus by hydrolysis and depolymerization of an unidentified component of the surface mucus. (2) It will produce ulceration in the alimentary tract of dogs when fed orally in doses which are comparable to those found in humans with chronic ulcerative colitis. (3) The mean lysozyme content of human stools from chronic ulcerative colitis patients is about twenty-seven times that of normal stools. (4) The lysozyme content invariably falls with improvement. (5) The colitic mucosa shows a nine-fold increase in lysozyme content over normal mucosa. (6) The mean daily output of lysozyme in chronic ulcerative colitis is 168 times that of normals.

We believe that these observations indicate that lysozyme is the etiologic agent which locally initiates the lesions of ulcerative colitis although we are in accord with the hypothesis that the basic difficulty may be psychiatric in nature.

On the basis of these findings we have begun therapy with anti-lysozymes, as noted by Dr. Meyer, at the Presbyterian and Roosevelt Hospitals. Two agents have been employed therapeutically, nisulfazole (paranitrosulfathiazole) and sodium hexadecyl sulfate.

Nisulfazole was introduced into the therapy of chronic ulcerative colitis by Dr. Ralph Major without knowledge of its anti-lysozyme effect. This property was discovered while screening compounds which had been reported effective in the therapy of the disease. This was the only agent exhibiting such anti-lysozyme activity to an appreciable extent. An inhibition of 42 per cent was noted in a concentration of

.0007 M. The mechanism of this inhibition is not yet understood.

Nisulfazole can be employed in 0.5 Gm. tablets or in 10 per cent suspension in pectin with oil of peppermint as a preservative. The former is for oral therapy, the latter for retention enemas and in occasional cases when it is desirable to pass a Miller-Abbott tube into the terminal ileum and administer the suspension through the tube.

I will not go into the details of oral therapy. By retention enema we give 100 cc. twice a day, once in the morning and once in mid-afternoon, and the patient lies in shock position from the time of his morning retention enema until supper time. He is up and about at other times. We give a low-residue, high-protein, high-calorie diet with vitamin supplementation. We make no effort to restrict particular foods unless there is undeniable evidence of allergy.

With oral therapy there are appreciable amounts of nisulfazole and sulfathiazole, its reduction product, in the blood. However, when administered by the Miller-Abbott tube technic and by retention enemas only traces are found.

Dr. Gellhorn treated twenty-one patients with chronic ulcerative colitis with nisulfazole, mostly with retention enemas. He noted remission in thirteen, equivocal responses in two and no improvement or progression in six. At Roosevelt Hospital we treated five patients with acute ulcerative colitis, with remission in four and no improvement in one. Statistically this is not dramatic but we believe that the worth of the drug is undeniable because of the extreme type of disorder treated. In several instances long-standing colitis has been arrested for the first time in years and the patient has given evidence of renewed vigor. In others what seemed to be a fatal downhill course seemed to be completely reversed. We have no data on the subsequent course of most patients treated with nisulfazole. The four treated at Roosevelt Hospital are in remission and have remained so up to nine months. That is a very short length of

¹ MEYER, K., GELLHORN, A., PRUDDEN, J. F., LEHMAN, W. L. and STEINBERG, A. Lysozyme activity in ulcerative alimentary disease. *Am. J. Med.* 5: 496, 1948.

time, of course. The follow-up study of the rest is under way.

Despite our belief that nisulfazole is a good therapeutic agent, the fact that nine of twenty-six patients did not respond made a search for a better inhibitor desirable. Such an agent was found in sodium hexadecyl sulfate, which Dr. Meyer has described and which, as he pointed out, inhibits lysozyme *in vitro* much better than nisulfazole. However, it has affinity not only for the NH_3^+ groups of lysozyme but of all proteins. This reduces the effectiveness of the compound below the test tube level where lysozyme is the only protein present; therefore, when using this drug one should prescribe a low-protein diet. Our practice has been to give 540 mg. of sodium hexadecyl sulfate every four hours around the clock. The drug apparently produces initial nausea, watery stools and epigastric pain in the majority of patients. These have subsided within two or three days in most instances but the drug apparently has irritative as well as therapeutic effects in some cases.

Our experience with sodium hexadecyl sulfate has been very limited as yet. We have treated eleven patients with ulcerative colitis, with complete remission in seven; two patients were definitely improved but continued to have loose movements despite a marked decrease in frequency; and two (with the highest lysozyme outputs) failed to improve. Of the seven patients showing complete remission, three suffered relapses but two of these responded to lower doses taken at home; in the third case subsequent treatment has not yet been attempted because of limited supplies of the drug.

On the basis of this brief experience we believe that anti-lysozyme therapy is a hopeful method of treatment for this very distressing disease and deserves further trial.

DR. ATCHLEY: Is there any work on the influence of the emotions upon the lysozyme titer?

DR. PRUDDEN: Yes, there is. Grace, Seton, Wolf and Wolff at Cornell recently pub-

lished² observations they had made on individuals with ulcerative colitis under varying emotional circumstances. They noted a marked increase in the lysozyme concentration of the stool and colonic surface mucus of these individuals at times of psychic stress. The number of observations was quite small; however, they were convincing. If this work is now confirmed by a large number of such determinations, it will be a very important contribution. Dr. Karush and Dr. Stewart in this institution are also studying the same problem.

DR. WALTER STEWART: Our results are not really worth mentioning yet. All we have done is to follow lysozyme titers in patients as we have treated them. It is our belief that if they are disturbed the titer goes up, and if not disturbed the titer goes down.

DR. ROBERT F. LOEB: I think this might be of some interest. The stools of patients with mucous colitis have been studied by Dr. Prudden and Dr. Meyer, if I am not mistaken, and do not show any increase in lysozyme, is that correct?

DR. PRUDDEN: That is correct, but only three patients have been studied. I do not think it is conclusive.

DR. LOEB: It seems to me that it would be important to extend that study; because if we assume that mucous colitis is of psychogenic origin and one finds that there is not an increase in lysozyme, in contrast with the patients who have developed non-specific ulcerative colitis, one might have a means of differentiating the psychogenic mechanisms.

DOCTOR: Are the diarrheas of specific etiology associated with increase in lysozyme?

DR. PRUDDEN: The only specific diarrhea that we have had the opportunity to assay was a case of amebic dysentery. The lysozyme content was 33 units per Gm. of stool. The upper limit of normal is at 9. We have not had any opportunity to do runs on

² GRACE, W. J., SETON, P. H., WOLF, S. and WOLFF, H. G. Changes in lysozyme formation in the human colon in various emotional states. *Bull. New York Acad. Med.*, 24: 390, 1948.

typhoid or the bacillary dysenteries. Plans have been made to obtain this type of specimen in the near future.

DR. ATCHLEY: Is there any relation between the motility of the bowel, or the state of the stool, and the lysozyme content?

DR. PRUDDEN: As a check we gave castor oil and magnesium sulfate to a fairly large number of patients. We found that there was only dilution of the lysozyme although the output for twenty-four hours increased slightly. This rise did not approach the increase in colitis.

DR. ATCHLEY: There are in ulcerative colitis a certain number of lesions which occur in regions remote or apparently unrelated to the colon. I have asked Dr. Fischel to discuss these observations in the hope that they may throw some light on the underlying processes operating to produce this disease.

DR. EDWARD E. FISCHEL: In this clinic during the past few years a number of cases of ulcerative colitis have been observed with extra-gut lesions, frequently of a rather spectacular nature. Erythema nodosum, purpura and other skin lesions have been seen, as well as arthralgias of varying severity. Occasionally the diagnosis of rheumatoid arthritis has been made. In addition the history of a previous bout of rheumatic fever has been noted in a few patients. These phenomena have been described by several authors but their incidence is variable, depending in part upon how much attention is focused exclusively on the gut. Extra-enteric phenomena are rarely mentioned in the voluminous charts of these patients unless pronounced changes occur.

Erythema nodosum has been described in about 1 per cent of the large series at the Mayo Clinic but other skin lesions such as pyoderma are much more frequent. Arthritis has been said to occur in about 4 to 6 per cent of the cases of ulcerative colitis in various clinics. In this hospital Dr. James Coss has recently reviewed eighty-five cases in which the work-up and subsequent study were considered adequate. A high incidence

of arthritis was found. Nineteen patients or 22 per cent had some degree of arthritis at some time in their course. Five of these had the diagnosis of rheumatoid arthritis on their charts but subsequent follow-up in most of these showed a degree of improvement that is not compatible with the usual course of untreated rheumatoid arthritis. The arthritis possibly is related to secondary infection which occurs so frequently in ulcerative colitis. It is of interest that bacteremias and, notably, bacillary dysentery give rise to arthralgias and arthritis. Seventeen of the eighty-five patients here had skin lesions of the various types mentioned.

The question arises as to the relationship of ulcerative colitis to the extra-gut lesions. It appears unlikely that the same process which initiates the colitis, whatever that be, also causes the arthritis and skin lesions. More probably these lesions are secondary to the inanition and bacterial infection that result from ulcerative colitis.

As Dr. Atchley mentioned in his opening remarks, it has been suggested that a specific bacterium causes ulcerative colitis. It is well known that various infections may cause diarrhea even if they do not directly involve the gastrointestinal tract. Thus infection of the upper respiratory tract in children gives rise to that acute diarrhea which enjoys the paradoxical name of parenteral diarrhea. However, in ulcerative colitis no specific organism has been consistently identified. Infection appears to play a secondary role although it may be a very important one in the clinical course of the patient.

Where there is infection, particularly of an intermittent or chronic variety, it may be expected as a physiologic response on the part of the host that sensitization at distant sites occurs and histologic changes take place according to the pattern of the Arthus or tuberculin reactions, with variations depending upon the site of the reaction, e.g., the skin, around the blood vessels or elsewhere. Microscopic aggregations of acute or chronic inflammatory cells have been

demonstrated in many patients following infections with a wide variety of organisms. Such lesions impress us clinically, however, only when they are severe enough and superficial enough to become macroscopically visible. This is, of course, a variation of the old focal infection hypothesis but I need not point out that the infection in ulcerative colitis is hardly focal.

Allergic mechanisms have been thought to play a role in the development of ulcerative colitis, perhaps as they have been thought to play a role in almost any undefined disease. Gray and Walzer studied exteriorized segments of gut in monkeys and observed human colostomies and proctoscopies. The subjects were passively sensitized to an antigen such as peanut oil by the injection of serum from a sensitized individual, and the mucosa exposed to this antigen, either directly or by ingestion. A severe inflammatory reaction occurred. Erythema and a profuse outpouring of mucus took place. In some instances acute ulceration of the mucous membrane occurred. This has been taken as a rational basis for the search for food allergy in cases of ulcerative colitis and for the use of elimination diets in the management of this disease. Although it is known that food allergy may cause acute diarrhea, it is extremely unlikely that this is the underlying cause of all cases of ulcerative colitis inasmuch as elimination diets appear to have no greater or better effect than the customarily employed low-residue diets with non-irritating foods. However, allergy to the various bacteria invading the exposed surface of the colon is probably instrumental in contributing to the severity of an already established ulcerative lesion, both by local necrotizing action of the allergic type and by obstructing lymphatic return.

In summary, the extra-gut lesions of ulcerative colitis serve to focus our attention on the fact that this disease, with its inanition and almost constant secondary bouts of infection, involves many systems outside of the gut, either by direct metastatic infection, by increasing susceptibility to infection

or by a phenomenon of hypersensitivity. These secondary phenomena of infection, of necrotizing allergic reactions, may in turn augment the severity of the existing lesion.

DR. ATCHLEY: In the absence of a definite etiology or a completely comprehended mechanism one seeks forces that may influence the course of a disease non-specifically. For instance, in asthma certain patients are quite comfortable except when they are in an extremely dusty environment. These factors are not primarily etiologic but they effectively exaggerate the disease manifestations.

An example of this in ulcerative colitis is the effect of diet. An excess of roughage in the diet may represent an added burden for the inflamed gut and in certain cases is an important therapeutic consideration. An extraordinary case in this clinic tended to relapse during menstruation, with remissions in the intermenstrual intervals. After a long downhill course the ovaries were removed with spectacular benefit.

We come next to the most controversial and one of the most interesting aspects of the whole problem, namely, the influence of the emotions on ulcerative colitis. We know quite well that psychic trauma will apparently precipitate a relapse or increase the symptoms. There are many studies of the neurotic personalities found in these patients. Dr. Walter Stewart will discuss this field. I have told Dr. Stewart that if he prefers to classify the emotions as a specific etiological agent rather than as a factor influencing the course of the disease, we shall be very glad to have him do so and take the consequences!

DR. STEWART: The beginning of the psychiatrist's interest in the somatic aspects of medicine dates back to Walter Cannon's contributions concerning the effect of emotions on physiologic function. His studies started a type of psychophysiology. The effect of emotions on the gastrointestinal tract is, as you know, very great. This fact allowed the psychiatrists to get a toehold on this general subject and since then they have been doing some pretty fancy footwork

for which I have to bear the responsibility today.

The psychiatric contributions to the study of ulcerative colitis began in 1930 with a paper by Murray which was followed by a second paper later in the same year. He reviewed twelve cases of ulcerative colitis. He noted a dramatic relationship between emotionally traumatic experiences and the onset of disease twenty-four to forty-eight hours later signaled by bloody diarrhea. He also noticed that these patients were very dependent and emotionally infantile. From this he reasoned that since the infant's response to fear is diarrhea, perhaps that was the emotion affecting these patients. The marked dependency of the patients studied is illustrated by the fact that of seven male patients, six showed an unbreakable, strong, dependent tie to their mother. The seventh showed a comparable relationship to an older sister who acted as a mother substitute. None of the seven men were married.

The next paper was by Sullivan in 1936. He reported six cases studied with psychiatric technics and tried to outline the sort of personality that developed ulcerative colitis. Since then there have been many publications, the most outstanding of which are those of Daniels and Alexander.

I want to reiterate a point made by Dr. Atchley. When we elect to discuss a symptom such as bloody diarrhea, we may be dealing with a heterogeneous group when viewed from the point of etiology. Even in a group homogeneous from an etiologic point of view, we may be working with multiple etiologic factors. It then becomes not a question of one or another of the possible etiologic factors but a concatenation of many factors. In ulcerative colitis there may well be multiple causes that produce the disease, not just one etiologic agent. I think everybody agrees that this is a complicated disease and there is probably room for everybody in it.

Our present state of knowledge suggests that in about 75 or 80 per cent of the patients that we psychiatrists see it is

possible to elicit a fairly typical history of emotional problems which seem to play some role in the disease process. The evidence for this comes from three points. One is the precipitating factor, the emotionally traumatic experience that precedes the occurrence of the disease. The second is the similarity of the basic personalities of this group and of the type of adaptation to life which they show; and third is the fact that they give evidence of the presence of neurotic disturbances prior to the onset of their somatic illness.

I would like to deal with the third point first. Wittkower in 1938 published a report in which he studied the frequency of neurosis prior to the onset of the illness. He found that patients with ulcerative colitis had an extraordinarily high frequency of previous neuroses, well outside that of the normal population. This disproves the thesis often stated that neurotic manifestations in patients with chronic ulcerative colitis are secondary to their prolonged debilitative disease and consequent invalidism.

To understand the role of precipitating factors described as traumatic experiences, I would first like to list some of them. A patient has a fight with his mother and then develops ulcerative colitis, or he loses money and develops ulcerative colitis, or he gets married and then becomes ill. But, one might say, these experiences are ubiquitous. People are always fighting, losing money or getting married. This is true. But in order to understand the potency of these experiences you have to have some understanding of the type of personality on which these experiences operate.

As I suggested before, these are exceedingly dependent people. They have learned to exist by leaning on somebody else; so when a potential ulcerative colitis patient has a fight with his mother and if she is the one on whom he was leaning, this takes on extraordinary meaning to him. It would be hard for you and me to understand the significance of the experience to him. Similarly, if he is a dependent person and the loss of money threatens his security, that

can have catastrophic meaning to him. Or, if he marries or becomes a parent, that is a tremendous increase in responsibility and in a negative sense threatens his dependency. He is forced to make a more mature adaptation than he has made before. To generalize this, one can say that these experiences are a threat to the dependency relationship on which these people depend for their existence.

Now what I will try to do is to give you a sort of outline of the typical personality of the ulcerative colitis patient. You will probably never find all of these factors in any one patient and you certainly will find some patients that have none of them. When you come across a patient who has none of the characteristics that I am going to describe you might argue that I am therefore wrong. I would argue the exception proves the rule; mainly it is evidence of our incomplete understanding. The final word on this has not been written at all; just the opening chapters of it are beginning to be understood.

Typically, the father of the child who is later going to develop ulcerative colitis is likely to be aggressive, dominating, frequently abusive or brutal. The child is consequently overtly fearful. The mother is likely to be a dominating, coercive, possessive and overprotective person. The child has to decide early in life how to handle these two problem parents. Generally, he settles for keeping away from the father and being submissive to the mother. He can rely on her strength as long as he agrees to her terms. He elects to be submissive in order to achieve a dependency relationship. He becomes submissive and agreeable at the expense of any rebellion. In effect, he achieves security through loss of freedom.

These patients are generally of high intelligence. In one series, 80 per cent were found to have an I.Q. of 115 or above. They are generally physically immature. The men have high voices, generally little body hair. The women are small breasted and generally narrow-hipped. Not only are they both physically immature but also emotionally

immature. As I have described, they are dependent upon one of the parental figures, most frequently the mother. They are methodical, precise, neat, meticulous and overly clean. They do not think dirty thoughts nor use dirty language. They are of low energy, passive, self-centered or narcissistic and generally proud, hence sensitive. They are likely to brood or stew over an imagined insult. They generally do not marry at all, or if they do, they marry late after an indecisive courtship to someone who is older than themselves. They recreate the dependency pattern with their husband or wife. The outstanding emotion that is observable in these people is fear. It is a natural product of their submissiveness. They fear to lose the dependent relationship which they need of necessity to stay alive. They are generally tremulous, cautious, obsequious and cooperative. They try to please you but underneath this subservient quality it is easy to detect its opposite. They are likely to be critical, demanding and subversive. I think the two terms that describe it best are subservient but subversive. Their dreams are likely to be violent, which is another indication of the tremendous rage that is pent up inside of them. Even in their interests in daily life they show a morbid interest in murder and rape which gives an indication of their tremendous pent-up rage. Part of their fear that you see on the surface is the response to this unconscious rage which exists inside of them. They not only fear the loss of the dependency situation but they fear the threat that their own unconscious is to this dependency. The rage accumulates because of their submissive adaptation. Since they are not able to express anger, it accumulates inside of them. It becomes undue and chronic because it is not ever allayed and the theory at present is that it is discharged through the autonomic nervous system. For reasons we do not know, in these patients it hits the lower intestinal tract rather than the stomach or blood vessels and they develop diarrhea.

I wanted to mention briefly the analytic

contributions in this field. They seem bizarre and are often ridiculed. This is because they are difficult to understand unless you have had personal experience with the analysis of one of these patients. The analysts believe that one of the reasons the lower intestine is chosen to express this pent-up rage and fear is because in childhood the first fight that ever develops with this overprotective, coercive, dominating mother centers around the question of toilet training. The mothers are neat and meticulous and they try to get their babies clean early of course. It is a matter of prestige and also it is an economy of diapers.

The child who is forced to be submissive as a small baby in the question of feeding, completely at the mercy of his mother, for the first time feels his authority. He can either agree to be bowel-trained or disagree. Frequently they disagree and a tremendous, catastrophic fight or battle develops which the mother wins. The child is generally trained early, and from that time on has that traumatic event of childhood as a method of expressing indirectly his rage and fear.

In the few minutes left I will deal with the problem of psychotherapy. The simplest form of psychotherapy is reassurance. One may describe these people as having fear over rage; that is, manifest fear and sub-manifest or repressed rage. Therapy can act to reassure these people, reduce their fear and allow their rage to come through. So you get an emotional catharsis or ventilation, frequently directed first at mother figures, some distance from the mother, and moving toward the mother finally. Often they end up by being violently angry at the mother. By this time they are dependent upon the therapist who believes he has not done very much. This is the most frequent symptomatic cure from the psychosomatic point of view. The therapist substitutes himself for the mother. He is not as coercive; he is a little less dominating and not so possessive. From this dependency, he can draw back slowly with small amounts of independence interjected.

The problem of re-educating the patient out of the whole framework of dependence into the framework of independence where he becomes aware of his executive capacity is extremely difficult. The question of the desirability of analysis for these patients is unsettled. There is some evidence that analysis may be contraindicated. These patients are often very depressed when you see them with their illness. It is easy to explain this as secondary depression. Analytic evidence shows, however, that it precedes the onset of illness. Ulcerative colitis, unlike peptic ulcer, seems to be more closely related to the psychoses than neuroses, and analysis frequently uncovers material that the patient has not the resources to handle. In these cases, analysis may do more harm than good.

In closing I would like to read to you one paragraph which is a discussion taken from the journal, *Gastroenterology*. There were a group of people who talked over chronic ulcerative colitis and in the discussion later, Dr. Sullivan, to whom I referred earlier, said, "The observation with patients with ulcerative colitis suggests the following: What happened in 1929 on the 40th floor of the Empire State Building, a floor occupied only by brokers and bankers who were there when the stock market crashed? What happens to that dozen individuals up there? One of them steals from old women and children and goes to jail. Because he must continue to try to be a big shot and have plenty of money, he embezzles. Another one jumps out of the window because he cannot face life without money, and I understand you would have had to duck if you walked by there in 1929. A third turns to alcohol. What happens to the broker who has the peptic ulcer personality? There isn't a man in this room who has not seen that same misfortune befall patients with peptic ulcer. What do they do? They roll up their sleeves, go to work and make another million in six months or a year and of course, they get recurrences with hemorrhages or perforations. What happens on the 40th floor of

the Empire State Building to the man who has ulcerative colitis? He would never be there." He might have added he would have been home with his mother!

DR. ATCHLEY: The next step in the analysis of a disease is a consideration of the effects of the disease upon the individual who is so afflicted. In ulcerative colitis we find so many of these secondary complications that they can be mentioned only very briefly. Among the local effects are abscess, perforation, polyposis and carcinoma. The individual as a whole may develop malnutrition with genuine vitamin deficiencies; he may become anemic and occasionally dehydrated. Furthermore, the psychologic effect of this type of illness with its inhibition of normal life pursuits may set up a serious vicious circle. Treatment of these general secondary effects of the disease itself is sufficiently routine to require no further encroachment on our limited time.

The local complications of ulcerative colitis often require surgical intervention and in many instances it seems wise to consult the surgeon in relation to technics for interrupting the total downhill course of the disease. Dr. John Lockwood will present the surgical point of view.

DR. JOHN S. LOCKWOOD: I never like to be in the position of defending surgical treatment as opposed to medical treatment, which is the basis on which so much argument goes on in a disease of this type about which so little is known of etiology. Actually surgical treatment simply is carrying out operative procedures under circumstances in which the fullest possible advantage has been taken of everything beneficial in the category of medical treatment.

The use of surgery in ulcerative colitis is necessarily directed either toward attempting to reverse an otherwise hopeless situation by checking the progress of the disease, or to remove a hopelessly diseased structure which, if left in place, remains a threat to the further health and comfort of the patient. It is in that light that the use of surgical procedures in ulcerative colitis must be considered.

The efficacy of surgery obviously depends upon the stage of the disease at which the surgical procedure is carried out. There has always been a great deal of disagreement as to the timing of surgical intervention in ulcerative colitis. I am speaking now particularly of the acute case with a spiking temperature, massive diarrhea, rapid loss of blood, protein and electrolytes, and progressively downhill course. There has been a tendency on the part of some physicians to take an optimistic view in this situation, hoping for the remission which does sometimes occur with astonishing abruptness. The time they refer such a patient to the surgeon will depend in part upon their experience with a previous case or the strength of their faith in conservative measures. That makes the comparison of surgical results in different clinics very difficult.

Since a permanent ileostomy is to be avoided if possible, certainly no conscientious surgeon would advocate resorting to a surgical procedure in ulcerative colitis until he, as well as the physician, has been convinced that conservative measures had failed. However, I think we ought to recognize that now and for the indefinite future it is going to be necessary to resort to surgical procedures in cases which have failed to respond to other methods of treatment, however rational.

The first type of case in which I think surgery becomes practically an emergency procedure is the acute case with progressively rapid downhill course, with loss of blood, protein and electrolytes which has defied all efforts at correction. Just how long such a condition should be allowed to go on without surgical intervention is very difficult to define. Opinion in the recent past has been moving more and more toward earlier intervention with a limit of about seven to ten days for the really acute, fulminating episode. The only procedure which would be contemplated at such a time would be complete diversion of the intestinal current usually by ileostomy; although in the case of segmental involvement in which only the

rectum and sigmoid are involved, it may be possible to do a colostomy and thereby gain the advantage of colostomy over ileostomy. Under these circumstances ileostomy may be considered a desperate but sometimes unquestionably life-saving procedure. We have all seen patients who within a relatively few days of complete diversion of the fecal stream have shown subsidence of fever and of blood loss although they may continue to have purulent discharge from the rectum for many days or weeks thereafter. Ileostomy does make it possible to stop the progressive physiologic disintegration. Very likely this simply is the result of modifying the conditions as regard secondary infection in the colon. None of us believes that ileostomy is a direct attack on the etiologic factor of ulcerative colitis.

The other indications for surgical intervention, apart from the acute case, are the long persistence of subacute manifestations of the disease, with recurrent bouts of bloody diarrhea, inability of the patient to gain weight, inability to resume anything like a normal life. Under these circumstances the surgical procedure indicated is colectomy, either partial or total, depending upon the degree of involvement of the bowel. Usually colectomy means a permanent ileostomy.

Stenosis, shrinkage, scarring of the colon with the result that it loses its proper function is another indication for surgery, particularly since we know there is a certain incidence of carcinoma (estimates vary from 1 to 3 per cent) in these chronically infected colons. Finally, it is obvious that perforation and hemorrhage are other indications for emergency surgery in ulcerative colitis.

How successful an ileostomy is depends upon the patient's attitude; on the promptness and unremitting attention which the surgeon gives to the care of the skin; on the success with which the patient makes use of modern types of ileostomy bags which protect the skin and in many patients permit them to resume normal life; and on the degree to which the patient has responded

to his surgical treatment. Sometimes it is possible to close the ileostomy and to re-establish continuity of the intestinal current, probably in not more than 10 per cent of the cases. One recent contribution in this field from Johns Hopkins Hospital has been the successful performance of an anastomosis between the ileum and the anus itself, leaving the sphincter mechanism and providing a perineal ileostomy with natural sphincter function. It has been surprising that in the cases in which this operation has been done successfully, the patient develops what corresponds to a rectal pouch and is able to have normal stools.

In 1941, Elsom and Ferguson³ published the results of a careful follow-up study of fifty patients with ulcerative colitis. Dr. Elsom is associated with Dr. Miller in the Gastrointestinal Clinic at the University of Pennsylvania; Dr. Ferguson is a surgeon. They worked together as the physician and surgeon must do in the proper appraisal of results in this disease. In selecting their material they deliberately chose patients with severe disease, and we may take their word for it that they chose groups treated by medical means alone and those treated by medicine plus surgical intervention in a comparable fashion in order to yield comparable data. In this series of fifty patients twenty-three were treated with medical procedures alone. The mortality in the one- to twelve-year follow-up was 32 per cent in those treated by medical procedures alone whereas the mortality in the surgically treated group was 26 per cent. Of greatest importance is the appraisal of the state of health one to twelve years after operation, a period of observation which perhaps provides inadequate follow-up but enough to justify the authors' interpretations. In the medical group only two of the twenty-three could be considered to be asymptomatic; several were invalids. In the surgical group the great majority were stated to have had

³ ELSOM, K. A. and FERGUSON, L. K. Appraisal of medical versus surgical treatment of idiopathic ulcerative colitis. Follow-up data on 50 cases. *Am. J. Med. Sc.*, 202: 59, 1941.

good results. Only two of the twenty patients who survived said that if they had it to do again they would not have ileostomy. The other eighteen unequivocally stated that if they had to go through it again they would choose the ileostomy in order to be rid of the disability under which they formerly labored. All the results were classified either as fair or good in twenty of the twenty-seven surgically treated patients who had survived the follow-up period. The ability to work was also of interest. Only two of the medically treated patients had been able to resume their occupation whereas over half of those surviving ileostomy and colectomy had been able to return to their normal occupations. Of those who were not able to do their normal work there were none who could not do light work.

DR. STEWART: I should like to raise one question in connection with the report by Drs. Elsom and Ferguson. The fact that the medically treated group is made up of those that chose not to have surgery makes them questionable as valid controls. You wonder why they did not submit to surgery. Possibly it is a measure of the additional fear in which they live. This might lead to a less favorable prognosis and so the comparison of the two groups would be biased. Emotional factors do not seem to have been taken into account.

DR. LOEB: I would just like to express a word of caution in the appraisal of therapy in this disease. As Dr. Lockwood pointed out, remissions in ulcerative colitis are common and may be of very long duration. I do not think it is unusual to find patients who have remissions of anywhere from one to perhaps five or ten years' duration. On that account one has to be particularly careful with this group of patients, especially in view of the importance of the psychogenic factors which play a role when the patient feels that he is being helped by his doctor in any way whatsoever. By way of illustration, you will recall that for a number of years the reports from the Mayo Clinic in

relation to the vaccine of Bargen were most dramatic.

DR. GEORGE A. PERERA: Early in the disease the medical man will urge conservative treatment to which the surgeon will often agree. In the later stages of the disease, many surgeons believe that the process has become too advanced for the risks of an operative approach. Are there sufficient data on patients operated upon early in the course of the disease to justify a less conservative attitude at this point?

DR. LOCKWOOD: It would be my impression that the results of ileostomy would vary inversely with the duration of the disease; that an ileostomy done before advanced organic changes had taken place in the colon would be more likely to be successful than one performed late in the disease after extreme physiologic depletion and marked scarring of the colon had developed. Certainly ileostomy should not be performed in every patient who develops an acute bloody diarrhea. However, if the patient's condition continues to deteriorate from such a cause and if there is evidence of marked systemic reactions to the disease, one should not delay more than seven to ten days before resorting to ileostomy. This is a situation which calls for refined judgment and I doubt if there are sufficient statistics to provide a clearcut answer to the question.

DOCTOR: Dr. Lockwood, would you comment on surgical interruption of nerve pathways in ulcerative colitis, specifically vagotomy?

DR. LOCKWOOD: In connection with the possible role of the autonomic nervous system in this disease, there is an interesting experimental study going on now which has to do with the evaluation of vagotomy in the treatment of ulcerative colitis. Dr. Clarence Dennis of the University of Minnesota has now performed vagotomy in thirty patients with severe ulcerative colitis. Because it was recognized that this was a highly debatable procedure, only severe cases have been selected. In this series, many of whom have now been followed for periods of up to eighteen months, there has been no oper-

ative mortality. One patient is worse; four are no better and twenty-five are classified as definitely improved.

The rationale for this procedure is rather tenuous, based on the fact that if a pre- and post-ganglionic sympathectomy is performed to remove the abdominal ganglia, an acute ulcerative process follows in many instances, both in the experimental animal and in one or two instances in which it has been performed in man. In trying out vagotomy Dr. Dennis simply was applying the reverse of this mechanism. We have done three vagotomies here on two patients who had very active disease and on one with only subacute disease in which the main problem was complicating leg ulcers. These three patients are now all in remission. One has resumed his normal occupation working on a farm; one is asymptomatic as far as the colitis is concerned but is suffering with severe arthritis as a complication. Although our series here is too small to be of significance, the results of Dennis suggest the possibility that one might apply "psychotherapy with the scalpel" in a fashion similar to that which has been carried out in the treatment of peptic ulcer. Final results will be awaited with great interest.

DR. ALFRED GILMAN: If the autonomic nervous system is to be implicated in this syndrome, it seems to me a very simple procedure to take one or two patients and block off both the adrenergic and cholinergic nerves to the bowel with tetraethylammonium and find out what happens to the lysozyme titer and clinical state of the patient.

DR. PRUDDEN: We will try that.

SUMMARY

DR. FREDERICK K. HEATH: The manifold nature of the clinical picture of ulcerative colitis, from mild to severe; the admixture of other tissue responses such as dermatitis and arthritis; the tendency to important complications of anemia, malnutrition, abscess formation, perforation, polyposis and carcinoma; the lack of correlation between

symptoms and the presence of bowel lesions, and the ever present possibility of remission were discussed. The position was taken that the etiology of the syndrome was unknown and that multiple causes may exist. Infection was discarded as an initiating factor although it often plays a secondary role. The place of allergy is not clear but is rarely important. The significance of the emotions was emphasized. The usual patient with ulcerative colitis presents evidence of prior neurosis, has attacks after an emotionally upsetting event and exhibits a typical personality characterized by intelligence, immaturity, dependency, fear and well hidden rage.

Lysozyme was discussed as offering a possible clue to the mechanism of the intestinal phase of the syndrome. The enzyme in man is a basic protein of low molecular weight with the ability to destroy by hydrolysis a specific but not yet identified acid mucopolysaccharide of the intestinal mucus or mucosal cell. It is present in high concentration in the normal pyloric mucosa. The enzyme has been shown experimentally to be capable of denuding the mucosal surface of its protective layer of mucus and may thus initiate the ulcerative lesion. The mucosa and stools of patients with ulcerative colitis contain much larger amounts of lysozyme than in normal subjects or patients with other types of diarrhea. Further, the concentration in the stools of patients with ulcerative colitis varies with their emotional state and falls with improvement in symptoms.

The lysozyme hypothesis also offers a therapeutic approach. Thus it has been shown that nissulfazole and the alkyl sulfates inactivate the enzyme not only in the test tube, but in more than two-thirds of patients with severe ulcerative colitis treated with either of these substances improvement in symptoms and fall in the stool level of the enzyme have resulted. As yet insufficient data are available to permit definite conclusions.

The possible role of the autonomic nervous system in the syndrome as a mediator of

impulses necessary to activate the enteric mechanism, whether this be lysozyme or some other as yet unknown agent, was suggested by the experimental surgical trial of vagotomy.

More clearly defined perhaps is the conventional surgical approach to the disease. When deformity of the colon, polyposis or possible carcinoma exist, some type of resection is indicated. Infection, such as abscess or perforation with peritonitis, demands surgical care. Many individuals with long continued disease not responding to other measures come to surgery by default. Others with severe acute disease may be candidates for ileostomy or colostomy, depending upon the site of the lesions, early in their course. Good results have been reported in all of these instances

in a sizeable proportion of cases. The presence of an ileostomy has been a less serious problem when careful preoperative information and postoperative instruction and care have been given.

However, if surgery has been decided upon, it appears clear that it should be considered before it is too late. The ultimate mortality figures in surgically treated patients are no higher than in medically treated groups but surgical intervention may become beyond the tolerance of a severely debilitated patient.

Yet the prospect of remission which remains utterly unpredictable as to its occurrence and duration continually beclouds all investigative and therapeutic efforts so that evaluation of data remains difficult.

Clinico-pathologic Conference

Anorexia, Weakness, Prostration and Death*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, O. H., (B. H. No. 161061), a fifty-one year old, white, married, carpenter's helper, was admitted to the Barnes Hospital on July 7, 1948, in a terminal state. No history could be obtained from him and the following limited information was given by his wife: The patient had apparently enjoyed perfect health until two months before entry at which time he noted the onset of anorexia. Concomitantly, painful bleeding hemorrhoids appeared and several weeks later the patient consulted a physician who performed a hemorrhoidectomy in his office. Shortly after the operation the patient returned to work but anorexia and rectal pain persisted and progressive weakness was noted. After working for one week the patient was unable to continue.

He again consulted his physician who told the patient that he probably had "cancer of the stomach," and the patient went to the Out-patient Clinic of the Barnard Free Skin and Cancer Hospital. Examination there revealed an ulcer 2 by 2 cm. in the posterior portion of the anus at the mucocutaneous junction which was said to have resembled a squamous cell carcinoma. Upon digital examination a questionable soft tissue mass was felt on the anterior wall of the rectum. He was advised to enter the hospital for further study but no bed was available; therefore, his name was placed on the waiting list. He began to have pain in the upper mid-abdomen which was constant but unrelated to position, movement or ingestion of food;

at no time was the pain severe. Anorexia and weakness increased, however, and in the week prior to admission during which the patient was able to take practically no food a state of prostration developed. In the two months he was ill he had lost approximately 25 pounds, but no change in the color of his skin had been noted nor had he had any diarrhea. On the day of admission he was brought to the Washington University Clinics and immediately sent into the hospital.

At the time of entry his temperature was 38.2°C., pulse 80 and respirations 32; his blood pressure was unobtainable. The patient was extremely cachectic and appeared ten to fifteen years older than his stated age. He was markedly dehydrated and hiccupped frequently. His skin was brown and dusky in color but there was no localized pigmentation. The mucous membranes of the conjunctivae were pale; the sclerae were muddy. The lips were slightly cyanotic and there was minimal pigmentation of the mucous membrane of the lower lip. The pupils reacted normally to light and accommodation and the optic fundi appeared normal. The mouth was edentulous and the tongue dry. The trachea was in the midline. Examination of the lungs revealed them to be clear to percussion and auscultation. The heart was not enlarged to percussion. The rhythm was regular; there were no murmurs but the sounds were distant. The abdomen was flat and tense. No masses could be felt and there was no edema. No generalized glandular enlarge-

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

ment was noted. Because of the patient's extremely critical condition further examination was deferred in order that treatment might be begun.

Limited laboratory data were as follows: Hemoglobin, 15 Gm. per cent; white blood cell count, 7,000; urinalysis: no specimen could be obtained. Blood chemistry: non-protein nitrogen, 42 mg. per cent; sugar, 214 mg. per cent (blood obtained after administration of intravenous glucose); chloride, 80 mEq./L.; total protein, 7.1 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 3.8 Gm. per cent.

As soon as the patient reached the ward 5 per cent glucose in saline was administered intravenously into one arm and plasma into the other. The pulse seemed to become stronger but after approximately 500 cc. of glucose and 250 cc. of plasma had been infused the patient suddenly had a convulsion and expired.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: I should like to begin our discussion today by asking if any student cares to commit himself in regard to the diagnosis.

MR. DONALD GREAVES: In view of the marked anorexia and the physical findings at the time the patient was examined at the Barnard Hospital, I should like to suggest carcinoma of the rectum with metastases to the liver. Such striking anorexia often indicates liver involvement.

DR. WOOD: Does marked anorexia suggest an hepatic lesion to you, Dr. Shank?

DR. ROBERT E. SHANK: Yes, I would agree that anorexia frequently is an important symptom of hepatic disease.

MR. LAURENS WHITE: I think that the patient had adrenal insufficiency, the severe, rather acute anorexia being explained by the low serum chloride.

DR. WOOD: What pathologic lesions should be considered?

MR. WARREN FELTON: Tuberculosis, idiopathic atrophy or carcinoma might have caused adrenal failure.

DR. WOOD: How would carcinoma lead to adrenal insufficiency?

MR. FELTON: It would of course have had to involve both adrenals.

DR. WOOD: If there are no other suggestions, we shall consider carcinoma of the rectum with metastases to the liver and adrenal insufficiency of a cause as yet undefined. Dr. Scheff, you will remember that this patient, in addition to his anorexia, was bothered by hemorrhoids. Is there any connection between these two complaints?

DR. HAROLD SCHEFF: I do not think so.

DR. WOOD: If this patient had come to your office with these complaints, would you have recommended hemorrhoidectomy?

DR. SCHEFF: In such a situation as this I would have first obtained a complete gastrointestinal x-ray series. Further, stool examinations should have been done for occult blood and parasites. The soft tissue mass which was described on the anterior wall of the rectum when the patient was examined at the Barnard Hospital was probably not significant. Had it been a carcinoma the mass should have been very hard and indurated.

DR. WOOD: Then you would have instituted more complete studies because of the fact that his presenting complaints, particularly the anorexia, were not explained satisfactorily by the presence of hemorrhoids.

DR. SCHEFF: That is correct.

DR. WOOD: I think it is very important for us to emphasize this point since the most obvious operable lesion does not necessarily represent the patient's major problem. Dr. Duden, would you discuss the anal ulcer which this patient had and comment on the etiology of ulcers in the lower portion of the gastrointestinal tract?

DR. CHARLES W. DUDEN: A very common type of anal ulcer in patients with hemorrhoids is that which arises as a result of local venous thromboses. Ulcerative colitis must also be considered.

DR. WOOD: Is carcinoma a possibility?

DR. DUDEN: The site involved here is not common for carcinoma of the rectum. This type of lesion which was located at the

mucocutaneous junction brings to mind an epithelioma.

DR. WOOD: This patient apparently did not develop the ulcer until after hemorrhoidectomy. Is such a sequence of events common after that operation?

DR. DUDEN: Interestingly enough, the converse may hold; that is, an ulcerative lesion about the rectum may lead to thromboses of the hemorrhoidal vessels, and not infrequently hemorrhoidectomy is performed without the basic lesion having been recognized. I would not be at all surprised if such were the case here.

DR. WOOD: Dr. Kenamore, do you believe that this patient had a malignant lesion of the lower bowel?

DR. BRUCE D. KENAMORE: I think it possible but unlikely. Although he was examined in the out-patient department of the Barnard Hospital where clinicians, who have had a wide experience with carcinoma, suggested that diagnosis, the entire clinical picture does not seem consistent with such an interpretation. I should like to point out in passing that the hemorrhoidectomy was performed without due consideration of the patient's general status.

DR. WOOD: Should hemorrhoidectomy be done in office practice?

DR. KENAMORE: I believe strongly that it should not.

DR. WOOD: Is it not done frequently by physicians in their offices?

DR. DUDEN: Yes, that is unfortunately true.

DR. WOOD: Dr. Kenamore, since you think that this patient probably did not have carcinoma of the lower bowel, can you offer any alternative suggestion?

DR. KENAMORE: I believe that the ulceration was more suggestive of tuberculosis or possibly amebiasis. The history is not in keeping with amebiasis but occasionally the course may be atypical.

DR. SCHEFF: It is difficult for me to believe that this man developed the anal ulcer immediately after his hemorrhoidectomy; in that event, he certainly would have had more difficulty postoperatively.

DR. WOOD: Do you think he may have had carcinoma?

DR. SCHEFF: No, an inflammatory lesion such as tuberculosis seems more likely to me.

DR. WOOD: I heard Dr. Hunter say before the conference that he had worked out a complete diagnosis for this case.

DR. THOMAS H. HUNTER: I have been "scooped" by one of the students. I had in mind the suggestion, already put forth, that this patient had a malignant lesion of the gastrointestinal tract with metastases to the liver and to both adrenal glands, with resultant adrenal insufficiency. He had marked anorexia and weight loss, both of which point to an upper gastrointestinal neoplasm. I agree that most of the evidence does not favor carcinoma of the lower intestine.

DR. WOOD: Exactly what site in the gastrointestinal tract did you have in mind?

DR. HUNTER: The stomach particularly.

DR. WOOD: Does that possibility appeal to you, Dr. MacBryde?

DR. CYRIL M. MACBRYDE: I think it is a good one; it must be remembered, however, that carcinoma with adrenal failure is very rare whereas tuberculosis of the adrenals is quite common. Next to tuberculosis I should think of other forms of infection. The fact that this patient became much worse soon after hemorrhoidectomy brings to mind the possibility that he may have developed infection at the operative site which subsequently spread to involve the adrenals.

DR. WOOD: Then in addition to Dr. Hunter's suggestion of metastatic carcinoma of the adrenals you would add tuberculosis or pyogenic infection. Do you believe that this patient had true adrenal insufficiency?

DR. MACBRYDE: He certainly died in a state that simulated adrenal insufficiency. He was severely dehydrated, in shock and hypochloremic. All of these findings are compatible with acute adrenal cortical failure.

DR. WOOD: Dr. MacBryde, what further data would be helpful had they been available? It is clear that this patient died so

soon after entry that complete studies were impossible.

DR. MACBRYDE: Blood potassium and sodium determinations would certainly have been of value.

DR. WOOD: Would not the carbon dioxide combining power and the serum chloride, taken together, have been of some value in a situation such as this?

DR. MACBRYDE: I would prefer to have sodium and potassium determinations.

DR. WOOD: I agree that those two would have been most valuable; on the other hand, measurement of carbon dioxide combining power is relatively simple to carry out and that value, taken with the serum chloride, enables one to estimate the blood sodium as a first approximation. When the flame photometer becomes readily adaptable for routine clinical determinations, it will serve as a most valuable aid in cases such as this. Dr. Moore, would you comment on the blood count in Addison's disease. Would a differential count have been helpful?

DR. CARL V. MOORE: A relative lymphocytosis is seen in adrenal insufficiency but such a change is not diagnostic; of more value possibly is the eosinophil determination which has recently been described by Thorn and his co-workers.¹ In a moribund patient, however, none of the diagnostic studies is very reliable.

DR. WOOD: Gastrointestinal malignancy is one of the diagnoses under consideration. Do you believe that hemoglobin of 15 Gm. is consistent with such a lesion?

DR. C. V. MOORE: The patient was markedly dehydrated. If he had survived until adequate hydration was achieved, his hemoglobin might actually have been only 10 Gm. instead of the 15 Gm. recorded.

DR. WOOD: Dr. Moore's answer indicates how carefully one must evaluate all laboratory data, particularly in a case such as this one. Although the blood sugar was re-

corded as 214 mg. per cent, we cannot be certain that this patient on admission was not indeed hypoglycemic, since he received an infusion of glucose before the blood sugar determination was performed. And now Dr. Moore points out that the hemoglobin of 15 Gm. per cent may well represent an apparent rather than a real value in view of hemoconcentration. Laboratory data may be most misleading unless properly evaluated in the light of the particular circumstances under which they are obtained.

STUDENT: I should like to know if the rapid downhill clinical course is compatible with a diagnosis of carcinoma of the body of the pancreas.

DR. DUDEN: I have never seen a patient with carcinoma of the pancreas fail as rapidly as this man did.

DR. WOOD: The fulminating nature of this man's illness favors adrenal insufficiency which may progress very rapidly indeed. Before we finish our discussion of the blood chemical findings I think it would be well to point out that the electrolyte changes might have been due to the fact that the patient had been vomiting. The electrolyte changes in Addison's disease may be simulated by the vomiting of prolonged pyloric obstruction. However, Gamble has compared the electrolyte changes in pyloric obstruction and in Addison's disease and has shown that there are significant differences.² For example, in Addison's disease the total base is depressed whereas the total base is not significantly depressed in pyloric obstruction. The carbon dioxide combining power, which was not determined here, would have been of value in differential diagnosis since in excessive vomiting due to pyloric obstruction the carbon dioxide combining power is often elevated whereas in Addison's disease it is decreased.

DR. ROBERT J. GLASER: I should like to ask whether the lesion in the rectum was described at the time that the patient was

¹ THORN, G. W., FORSHAM, P. F., PRUNTY, F. T. G. and HILLS, A. G. A test for adrenocortical insufficiency. The response to adrenocorticotrophic hormone. *J. A. M. A.*, 137: 1005, 1948.

² GAMBLE, J. L. *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*. 5th ed. Cambridge, 1947. Harvard University Press.

admitted to this hospital. Was a rectal examination done?

DR. WOOD: Because this patient was in a terminal state when he entered the hospital, a complete examination could not be done. Dr. Chernoff, do you have any information in answer to Dr. Glaser's question?

DR. AMOZ I. CHERNOFF: No, I do not. As you have stated, because of the patient's extremely critical condition, the rectal examination was omitted.

DR. I. JEROME FLANCE: I think it would have been very unusual for the anal ulcer to have been due to carcinoma in view of the fact that this patient had no symptoms two months prior to his death. Similarly, in regard to tuberculosis, patients who have tuberculous ulcers of this size at the mucocutaneous junction of the rectum and anus in general have widespread tuberculosis involving other organs and exhibit signs of systemic illness over a longer period of time than did this man.

DR. KENAMORE: I would agree with Dr. Flance's comments. I have never seen a tuberculous ulcer associated with carcinoma but they are reported. There are, however, occasional cases of gastrointestinal tuberculosis apparently unassociated with systemic tuberculosis, just as in Addison's disease there may be no pulmonary tuberculosis.

DR. WADE: I do not think proper cognizance has been taken of the total protein, albumin and globulin determinations. The globulin was definitely elevated and that finding, in combination with hemorrhoids, anorexia and weakness, is compatible with a diagnosis of cirrhosis of the liver. Further, patients with cirrhosis may die in as short a time as this patient did. Despite the fact that some of the blood chemical findings suggest adrenal insufficiency, it is not particularly unusual for a patient with rapidly progressive cirrhosis to exhibit a similarly rapid downhill course, with a clinical picture suggesting adrenal exhaustion.

DR. WOOD: How many patients with cirrhosis have you seen die as rapidly as this man did without jaundice?

DR. WADE: Not many, but jaundice is often not severe in advanced cirrhosis and the statement was made here that this patient did have muddy discoloration of the sclerae.

DR. WOOD: Dr. Chernoff, did you think that the patient was jaundiced?

DR. CHERNOFF: I was certain he was not jaundiced but his skin color was not normal. It was brownish-yellow and I can best describe it as being of a coppery cast.

DR. WOOD: Dr. Taussig, does this picture suggest cirrhosis of the liver to you?

DR. BARRETT L. TAUSSIG: Cirrhosis is a possibility but it is difficult for me to understand how a patient without an alcoholic history could die from liver failure in two months after being apparently perfectly well.

STUDENT: I should like to know whether the albumin and globulin values are consistent with the diagnosis of Addison's disease.

DR. WOOD: The globulin was 3.8 Gm. per cent and the albumin 3.3 Gm. per cent. Are such values compatible with a diagnosis of adrenal insufficiency, Dr. MacBryde?

DR. MACBRYDE: They are certainly not characteristic of Addison's disease.

DR. WOOD: Would chronic infection explain them, Dr. Harford?

DR. CARL G. HARFORD: Chronic infection is often associated with hyperglobulinemia. Among the chronic infections one must certainly include tuberculosis.

DR. DUDEN: It seems conceivable to me that a less common type of tumor may have been present here. A rapidly growing neoplasm such as melanosarcoma would be consistent with a rapid downhill course and widespread metastases through the abdomen which conceivably could have involved both adrenals. I think whatever type of neoplasm he had, if indeed he had one, involved both adrenals.

DR. VIRGIL SCOTT: Why did the patient have a convulsion?

DR. MACBRYDE: One of the manifestations of acute adrenal insufficiency is disturbance in the central nervous system.

Many patients with Addison's disease actually die in epileptiform attacks, presumably on the basis of hypoglycemia.

DR. SCHROEDER: In view of the fulminating course in this case I should like to ask Dr. MacBryde if he does not think that tuberculosis is an unlikely cause of the adrenal failure.

DR. MACBRYDE: In many patients with adrenal insufficiency tuberculosis is not recognized until postmortem examination. I do not believe that the course of the adrenal insufficiency is particularly helpful in determining its cause.

DR. JOSEPH C. EDWARDS: I should like to ask the gastroenterologists to comment on the relation of diarrhea to gastrointestinal malignancy.

DR. DUDEN: Diarrhea is found in association with carcinoma of the rectum in approximately 18 to 20 per cent of the cases but more commonly constipation is seen. Those figures include carcinoma of the sigmoid and descending colon as well. Diarrhea is much more frequent when the malignancy involves the cecum and ascending colon but it certainly does not occur in over 50 per cent of those patients.

DR. WOOD: I should like to summarize the suggestions made by the students and by the staff before Dr. Moore presents the pathologic findings. If I sense the opinion of the group correctly, most of the staff members favor acute adrenal insufficiency caused by a lesion in the adrenal glands, presumably on the basis of tuberculosis or some other infection. The possibility of gastrointestinal malignancy with metastases to both adrenals has also been advanced as a cause of the adrenal insufficiency. The etiology of the anal ulcer remains obscure. The final clinical diagnoses made by the house staff at the time of the patient's death were as follows: ?adrenocortical hypofunction; ?neoplasm of unknown site.

Clinical Diagnoses: Acute adrenal insufficiency, ?due to tuberculosis or other infection; ?gastrointestinal malignancy with metastases to both adrenals; ?tuberculous

ulcer of the mucocutaneous junction of the anus.

PATHOLOGIC DISCUSSION

DR. F. BERTOLI: Advanced emaciation, pallor and a diffuse grayish brown discoloration of the skin were observed at the time of autopsy. No ulcerations were present on the skin surface.

Both pleural cavities were obliterated by dense fibrous adhesions over the superior portions of the upper lobes of the lungs and on each side there was a small amount of clear, straw-colored fluid. The lungs weighed 640 Gm. Upon section of the right lung numerous extensive areas of caseation, marked fibrous thickening of the interlobar stroma, grayish pink, rubbery parenchyma and scattered miliary tubercles throughout the upper lobe were exposed. The middle and lower lobes contained numerous foci of caseation and round, grayish yellow, gritty, calcified nodules measuring 1 or 2 mm. in diameter. A moderate amount of frothy fluid was present in the remaining parenchyma.

The tracheobronchial and bronchopulmonary lymph nodes were enlarged, black and edematous with small caseous and calcified nodules. A secondary branch of the pulmonary artery leading to the upper lobe of the right lung was partially obstructed by a grayish red thrombus firmly attached to its wall. The left lung contained similar but less advanced pathologic changes.

The heart which weighed 280 Gm. was of normal size and appearance.

The peritoneal cavity contained a small amount of clear yellow fluid and was free of adhesions. The spleen was slightly enlarged, weighing 200 Gm. The capsule was smooth and taut, and the pulp was abundant, dark red and firm; a few scattered calcified nodules 1 mm. in diameter were noted and the follicles were prominent. The liver weighed 1,950 Gm. The peritoneal surface was smooth and glistening and the cut surface smooth, firm and reddish brown with a prominent lobular pattern. The

kidneys, which weighed 180 Gm. each, were slightly granular on their cortical surfaces.

The adrenals were approximately three times normal size; the right weighed 26.5 Gm. and the left 38 Gm. They were covered by thick fibrous capsules. On section each presented a smooth, grayish yellow, firm, rubbery surface with dark red streaks and blotches.

The stomach, duodenum and pancreas were not remarkable. The distal portion of the ileum contained a deep, oval ulcer in the mucosa 2.5 mm. deep; it had thick elevated borders which were studded with small tubercles and its base was dark red and covered with grayish yellow debris. The ulcer extended through the muscularis to the serosa which was likewise studded with small tubercles arranged in a linear pattern along the course of the lymphatics. In the adjacent mucosa and in the mucosa of the cecum there were numerous shallow ulcerations measuring 1 cm. in diameter with tiny tubercles about their borders. The corresponding mesenteric lymph nodes contained foci of caseation and some were replaced by a tough, grayish yellow tissue. White streaks accompanied by tubercles could be traced across the mesentery from the intestine to these nodes.

The bladder and prostate were not remarkable. The right seminal vesicle was moderately enlarged and had a gray, thick wall which contained abundant loculated yellow, thick, granular material. The left seminal vesicle was not unusual. The vasa deferens and testes were not remarkable.

The brain was not examined. The sternal, costal and vertebral bone marrow were not remarkable.

DR. ROBERT A. MOORE: On the basis of the gross findings, it seemed apparent there was tuberculosis involving particularly the lungs, intestines, right seminal vesicle and adrenals. When, however, Dr. Margaret Smith reviewed this case shortly after the autopsy was performed, her astute knowledge of gross pathology enabled her to recognize that there were atypical

changes in the adrenal glands; they were too yellow and their consistency was rubbery rather than friable as is the case in tuberculous caseation. Consequently, a frozen section was ordered and an additional very interesting suspected diagnosis was immediately confirmed. The first section (Fig. 1) is from a paraffin block prepared later from the same tissue as the original frozen section. It represents all the adrenal gland which remained. From this and other sections it seems probable that 90 to 95 per cent of the adrenal cortex had been destroyed. This photomicrograph shows the edge of one of the foci of necrosis; about these foci there were large macrophages but no true tubercles, epithelioid cells or giant cells. With higher magnification (Fig. 2) it can be seen that these large macrophages were filled with round organisms with surrounding halos. The appearance, size and location of these organisms was so typical the diagnosis of histoplasmosis of the adrenal glands was established.

I want to point out that the diagnosis of histoplasmosis was not made unequivocally by Dr. Smith, but the gross appearance of the adrenals aroused her suspicions and led to the prompt search for some other diagnosis than tuberculosis. I emphasize this approach first to give credit to Dr. Smith for having suspected the correct diagnosis and, secondly, to reiterate what I often tell the students and staff, namely, that there is still a science of gross pathology. One does not need a microscope to make every diagnosis.

Despite the hours which had elapsed from the time of autopsy till the frozen section was prepared, material was taken from the adrenal in an attempt to culture the organisms; even in the face of the gross contamination that had occurred Dr. Parker Beamer was able successfully to isolate typical cultures of the fungus.

Despite this fascinating and rather startling finding, it must not be forgotten that most of the lesions were of a different nature. Figure 3 is from the lung and presents a

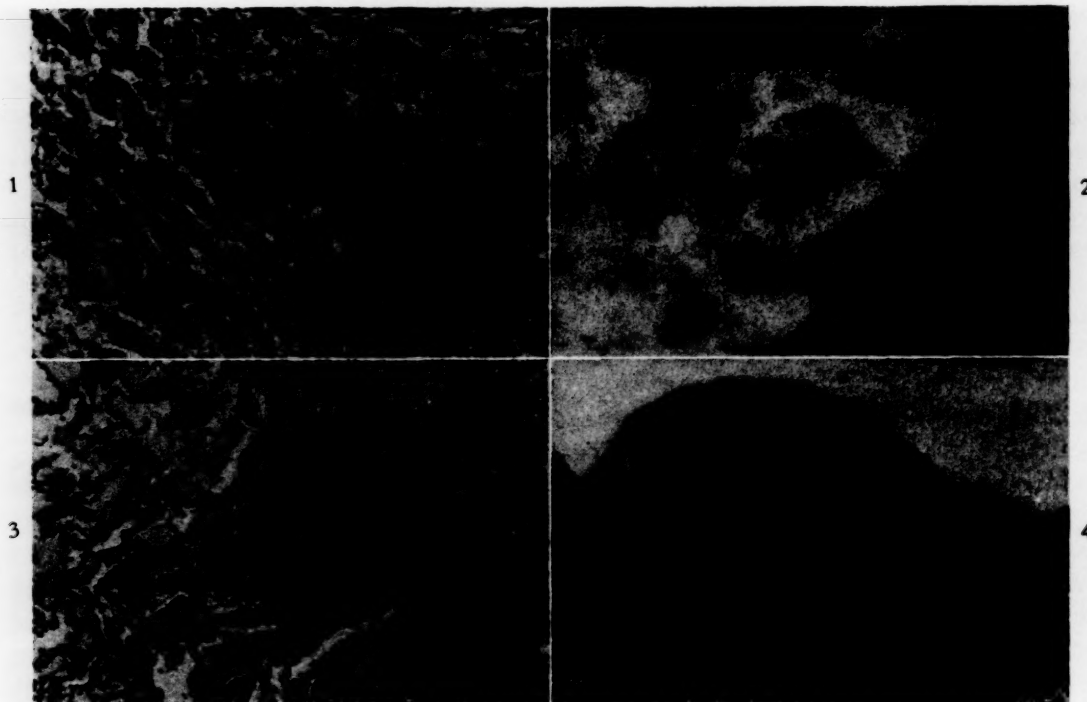


FIG. 1. Section of the adrenal showing a small amount of normal cortex and a granulomatous reaction about a focus of necrosis.

FIG. 2. Oil immersion photomicrograph showing *Histoplasma capsulatum* within macrophages in the adrenal.

FIG. 3. Fibrocaceous tuberculous lesion in the lung.

FIG. 4. Edge of a tuberculous ulcer in the ileum. The base of the ulcer lies to the left of the illustration.

lesion with all the histologic characteristics of tuberculosis. There is a central caseous focus at the right of the photograph which is surrounded by epithelioid cells, lymphocytes, a typical Langerhans giant cell and fibroblasts.

In Figure 4 the margin of an intestinal ulcer is seen; the base lies to the left. The edge of the ulcer is elevated and covers a fibrous and granulomatous lesion in which there is the classical reaction to tuberculosis. Acid-fast organisms were demonstrated in the lesion by the Ziehl-Nielsen stain (Fig. 5); thus it is established that this patient had both tuberculosis and histoplasmosis. Figures 6 and 7 illustrate additional typical tuberculous lesions in the spleen and right seminal vesicle, respectively.

I think that the tuberculous involvement of the seminal vesicle explains the soft tissue mass described in the anterior wall of the rectum. At the time of autopsy the rectum

was examined from the outside, but the region of the mucocutaneous junction was not removed because of consequent technical difficulties in the repair of the body after such a procedure. We did not observe at the time of the autopsy any ulceration at the mucocutaneous junction.

Figure 8 is a section of the thrombus in the pulmonary artery showing that it was considerably organized and had been *in situ* for some time.

In summary, the anatomic findings indicate this patient had chronic tuberculosis involving the lungs, the intestine and the right seminal vesicle with a terminal miliary spread which was of no clinical consequence. This type of terminal spread is often observed in patients with chronic pulmonary tuberculosis and does not represent the disease entity of miliary tuberculosis. In addition there was histoplasmosis limited to the adrenal glands which brought about



FIG. 5. Rod-shaped, acid-fast organisms in epithelioid cells in the base of the ulcer in the ileum. (Oil immersion lens.)

FIG. 6. Tubercle in the spleen.

FIG. 7. Tuberculous inflammation of the right seminal vesicle.

FIG. 8. Partially organized thrombus attached to the wall of the pulmonary artery in the right lung.

sufficient destruction of the cortices to give the signs and symptoms of adrenal insufficiency.

Final Anatomic Diagnoses: Caseous and fibrocaseous tuberculosis of all lobes of the lungs, especially in the upper lobes, with foci of caseous pneumonia; caseous and fibrocaseous nodules in the tracheobronchial and bronchopulmonary lymph nodes, more marked on the right; fibrosis of the lungs, most advanced in the upper lobe of the right lung; tuberculous ulcers of the ileum and cecum with caseous necrosis of the wall of the ileum; caseous and fibro-

caseous tuberculosis of the serosal surface of the ileum and the adjacent mesenteric lymph nodes; focal granulomas of the liver and spleen; tuberculous seminal vesiculitis, right; histoplasmosis of the adrenal glands, with caseous necrosis (*Histoplasma capsulatum* cultured from postmortem tissues); partially organized thrombus in a secondary branch of the right pulmonary artery.

Editor's Note: Reprints of these conferences are now available. Requests should be sent to Dr. Robert J. Glaser, Department of Medicine, Barnes Hospital, St. Louis 10, Mo.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE EASTERN SECTIONAL MEETING

HELD IN PHILADELPHIA, DECEMBER 4, 1948.

MESENCEPHALOTHALAMOTOMY FOR RELIEF OF INTRACTABLE PAIN. *E. A. Spiegel, M.D. and H. T. Wycis, M.D. (Introduced by L. A. Soloff, M.D.), Philadelphia, Pennsylvania.* (From the Departments of Experimental Neurology and Neurosurgery, Temple University School of Medicine and Hospital.)

A lesion of the long ascending pain-conducting pathways in the mid-brain is combined with a lesion of the dorsomedial nucleus of the thalamus by means of a stereotaxic technic. Since patients become unconcerned about their pain following prefrontal lobotomy and since the dorsomedial nucleus of the thalamus degenerates following this procedure, the lesion of this nucleus is added to that of the long ascending pain-conducting pathways in order to induce a relative indifference to pain perceived through the remaining auxiliary pathways. In a patient suffering from unilateral facial pain for six years, despite retrogasserian rhizotomy, mesencephalothalamotomy on the opposite side abolished the pain completely except for occasional paresthesias in the maxillary region. In a second patient suffering from diffuse burning pain and spasms in the right lower extremity following injury to the lumbar spine and which was unrelieved by sympathectomy, rhizotomy and bilateral chordotomies, bilateral mesencephalothalamotomy reduced the painful area to the region around the right buttock while the spasms of the leg and the sensation of the muscular contractions persisted.

VOLUME CHANGES IN THE FUNCTIONAL DIVISIONS OF TOTAL BODY WATER FOLLOWING THERAPY IN HYPOTHYROIDISM WITH PERICARDIAL EFFUSION. *A. Sokalchuk, M.D., C. T. Bello, M.D. (by invitation), E. M. Greisheimer, M.D. (by invitation), and L. A. Soloff, M.D., Philadelphia, Pennsylvania.* (From the Depart-

ments of Physiology and Medicine, Temple University School of Medicine and Temple University Hospital.)

Recently four consecutive cases of myxedema with so-called "myxedema heart," usually attributed to a uniform dilation of all cardiac chambers, were found to have pericardial effusion on aspiration. With use of the dye T-1824, sodium thiocyanate and percentage change in cellular hemoglobin, estimations were made before and after therapy in three of the aforementioned cases on plasma volume, blood volume, "available fluid space," interstitial fluid volume and percentage change in the intracellular fluid volume. The small number of cases permits only a preliminary report at this time but since the total number of reported cases proven to have pericardial effusion by aspiration has been extremely meager, we believe we are justified in mentioning certain trends.

The plasma and blood volumes are low in these cases and tend to increase under therapy. To date no significant change in interstitial fluid volume has been observed. Changes in plasma volume are reflected in "available fluid space" measurements. Intracellular fluid volume appears to decrease under therapy.

TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE. *J. B. Johnson, M.D., Charles Ireland, M.D. (by invitation), R. F. Thomas, M.D. (by invitation) and Andrew Bass, M.D. (by invitation), Washington, D. C.* (From the Department of Medicine, Howard University Medical School.)

This report presents a study of eleven patients with hyperthyroidism who were treated with I-131. The diagnosis was based on clinical manifestations, basal metabolic rate, blood cholesterol and galactose tolerance test. Five of the patients were previously treated unsuc-

cessfully with other methods, including propylthiouracil, vitamin A or subtotal thyroidectomy. The ages ranged from twenty-two to sixty-three years. The basal metabolic rate during the week preceding therapy ranged from +35 to +90. One dose of I-131 consisting of 0.5 millicuries per estimated Gm. of thyroid was given. The basal metabolic rate and other tests of thyroid function were made at periodic intervals after treatment.

During the first week after therapy the basal metabolic rate fell precipitously in all cases. At the end of ten weeks eight of the eleven patients showed clinical remission, marked reduction in the size of the thyroid, normal basal metabolic rate and associated return of the blood chemical findings toward normal. Another patient required thirteen weeks for a clinical remission. In one patient observations have not been completed. One patient can be classed as unsuccessful. In five of the eleven patients the metabolic rate continued to fall, going below -15. In each of these five subjects the basal metabolic rate spontaneously returned to normal from the hypothyroid level within six to twelve weeks. No serious complications were encountered in any of the patients.

I-131 in adequate dosage is an effective drug in the management of hyperthyroidism. Exact dosage and the duration of remission with I-131 represent problems which are still unsolved.

A METHOD FOR MEASURING COMPARATIVE VELOCITIES OF THE CELLULAR AND FLUID COMPONENTS OF THE BLOOD IN THE PERIPHERAL CIRCULATION. *Edward D. Freis, M.D., Joseph R. Stanton, M.D. and Charles P. Emerson, M.D., Boston, Massachusetts.* (From the Evans Memorial Hospital, Boston University School of Medicine.)

A method is described for measuring the comparative velocities of red cells and plasma in a single circulation through an isolated portion of the peripheral vascular bed in man. With the circulation to the hand occluded, a mixture of plasma labelled with T-1824 and of red cells labelled by means of selective agglutination differences was injected instantaneously into the brachial artery. Simultaneously, and for one and one-half minutes or longer thereafter separate blood specimens were collected every two or five seconds from a large antecubital vein of the same arm. The concentration of the dye

T-1824 and of the donor cells was measured in each specimen and the respective curves of concentration plotted against time. Because of the relatively large concentration of labelled substances injected in respect to the volume of the vascular bed perfused, concentration of the dye and tagged cells removed at the antecubital vein could be measured with considerable accuracy.

Analysis of the time concentration curves so derived indicated that the mean velocity of the red cell mass consistently was greater than that of the plasma mass.

TREATMENT OF PERNICIOUS ANEMIA WITH CRYSTALLINE VITAMIN B₁₂. *Edward H. Reisner, Jr., M.D., (Introduced by Menasch Kalkstein, M.D.), New York, New York.*

Vitamin B₁₂, a crystalline cobalt complex isolated from liver, has been found to have tremendously high antipernicious anemia activity. It is believed to be the actual anti-anemic principle of liver. West and Reisner treated eleven patients with pernicious anemia in relapse with varying doses of B₁₂. Maximal reticulocyte responses were obtained from a single injection of as little as 6 gammas. The potency of the material as determined by these studies is slightly more than 1 international unit per gamma. Of the eleven patients five had combined system disease. The early cord lesions were completely relieved and later manifestations vastly improved by B₁₂ therapy. Vitamin B₁₂ sufficed to bring about full remission of the blood count in patients maintained on it. It is not known yet what the relationship is between B₁₂, pteroylglutamic acid and thymidine.

TREATMENT OF PRIMARY ATYPICAL NON-BACTERIAL PNEUMONIA WITH AUREOMYCIN. *Emanuel B. Schoenbach, M.D. and Morton S. Bryer, M.D., Baltimore, Maryland.* (From the Department of Preventive Medicine, Johns Hopkins University School of Medicine.)

Primary atypical non-bacterial pneumonia has been extensively investigated during the past seven years and no therapeutic agent has been found to influence the course of the disease. Ten patients with primary atypical non-bacterial pneumonia have been treated with oral aureomycin, a new antibiotic derived from cultures

of *Streptomyces aureofaciens*. These patients were ten to fifty-nine years of age and had been ill for one to nine days before aureomycin therapy was instituted. The diagnosis was established by history of non-productive cough, fever, headache, chills, positive x-ray evidence of pulmonary consolidation, relative leukopenia, essentially negative bacteriologic examination and by serologic studies. The latter included tests for the presence of cold agglutinins, agglutinins for the streptococcus MG, antibodies for Q fever, influenza and the psittacosis group on serial bleedings.

The patients treated with aureomycin became afebrile within twenty-four to seventy-two hours. Most patients were afebrile in less than forty-eight hours. In only one patient, with extensive involvement of four lobes, the temperature fell precipitously but did not become normal until seventy-two hours after institution of aureomycin therapy. The clinical response of these patients paralleled the rapid defervescence of fever. Convalescence was uneventful except for mild transitory thrombophlebitis in one patient and probable thrombosis and leukocytosis several days after the drug had been stopped in another. Both these patients had developed high titers of cold agglutinins during this period.

The drug was well tolerated and no toxic or untoward reactions were noted. The total amount of drug administered varied from 3.8 to 8.0 Gm. over a five to seven-day period. Aureomycin has not been noted to have an antipyretic effect in many other infections.

These results indicate that aureomycin may be a valuable therapeutic agent for the treatment of primary atypical non-bacterial pneumonia.

TUBERCULOUS PERITONITIS TREATED WITH STREPTOMYCIN. *Thomas McP. Brown, M.D. and Ruth H. Wichelhausen, M.D. (introduced by Joseph F. Sadusk, Jr., M.D.), Washington, D. C. (From the Medical Department, Veterans Administration Hospital.)*

Two patients with tuberculous peritonitis were treated with streptomycin and the clinical records of twenty-four additional patients treated in various Veterans Administration Hospitals were reviewed by the authors. Duration of treatment varied between 25 and 164 days; total dosage of streptomycin was between 43 and

349 gm. Response to treatment was manifested chiefly by subsidence of fever and ascites, amelioration of abdominal symptoms, a feeling of general well being and gain of weight. The peritoneal involvement responded favorably in twenty-four of twenty-six cases regardless of duration of symptoms prior to therapy. Several patients developed new tuberculous lesions elsewhere during or after streptomycin therapy but recovered clinically from the peritonitis.

Twenty-two of twenty-six patients had no significant abdominal symptoms after cessation of therapy. Two patients relapsed and responded to a second course of streptomycin. There were two deaths, one patient with pulmonary and peritoneal involvement failed to show definite response to therapy and the other showed temporary improvement with relapse and subsequent death when the drug was discontinued because of toxicity. In six of the patients who received less than 80 Gm. of streptomycin two deaths and one relapse were observed. There were no deaths and one relapse in the remaining twenty patients who received 86 Gm. or more of streptomycin. Follow-up observations have been possible in nineteen patients, ten have been followed for six to eighteen months and nine for less than six months.

Three patients were re-explored electively shortly after cessation of therapy and striking improvement was demonstrated. All three have remained clinically well for six to twelve months. Two biopsy reports are available. One patient showed no microscopic evidence of tuberculosis. The histologic diagnosis in the other was tuberculosis of the peritoneum.

The interpretation of the final results of streptomycin therapy in tuberculous peritonitis must await prolonged observation.

BCG VACCINATION IN SARCOIDOSIS. *Harold L. Israel, M.D., Maurice Sones, M.D. and Samuel C. Stein, M.D., Philadelphia, Pennsylvania. (From the Woman's Medical College of Pennsylvania and The Henry Phipps Institute of the University of Pennsylvania.)*

Since the relationship between sarcoidosis and tuberculosis remains questionable, an attempt was made to ascertain the response of patients with sarcoidosis to artificial inoculation with living, avirulent tubercle bacilli. Intracutaneous BCG vaccination has been per-

formed with cultures and technic that produces conversion to positive tuberculin reaction in 93 per cent of normal persons.

Eighteen patients with sarcoidosis have been vaccinated with BCG. Three of these patients early in the study had strong clinical and laboratory evidence to support the diagnosis but biopsy material was not available. More recently vaccination has been restricted to patients with typical histologic lesions. In many cases guinea pig inoculation of the material has been performed. Two patients have been vaccinated twice. Sixteen patients have been under observation for three months or more and have had tuberculin tests after vaccination. None became positive to first strength PPD, nine became positive to second strength PPD, three had doubtfully positive reactions to second strength PPD and four had negative reactions. Of the nine who had positive reactions five have subsequently changed to negative.

Preliminary results indicate an inability on the part of sarcoid patients to develop and maintain tuberculin allergy. Study is now in progress to determine whether this immunologic defect is specific or general.

SERUM COMPLEMENT IN RHEUMATIC FEVER AND OTHER CONDITIONS. *Edward E. Fischel, M.D., New York, New York.* (From the Department of Medicine, Columbia University College of Physicians and Surgeons and the Edward Daniels Faulkner Arthritis Clinic of The Presbyterian Hospital.)

Quantitative serial studies were made of total serum complement (C') in normal subjects and in various pathologic conditions, using the spectrophotometric technic for determination of the 50 per cent hemolytic unit with optimal concentrations of magnesium and calcium according to Heidelberger and co-workers. Repeat determinations gave values of ± 1.1 units.

The C' content of a series of normal sera was 37.6 ± 3.9 units per ml. Low C' levels (11-20 units) were found in certain allergic states such as serum sickness and also in acute glomerulonephritis. Gradual restitution of C' occurred with recovery. High C' levels (51 to 89 units) were found in some drug allergies, in thirty-one of thirty-three cases of rheumatic fever followed serially and in other febrile illnesses. Only two

patients with rheumatic fever were found with a low C' which gradually became normal. The elevated C' in rheumatic fever appears to be a sensitive criterion of activity of the rheumatic process. Occasionally recrudescences were seen with an initially normal sedimentation rate and an elevated C'.

The low complement level in serum sickness may be due to fixation of C' by an antigen-antibody complex. However, low levels in this and other conditions may be due to other causes, such as an increase in gamma globulin and other anticomplementary substances or a diminished production of complement.

REDUCTION IN CIRCULATING EOSINOPHILS FOLLOWING EPINEPHRINE, INSULIN AND SURGICAL OPERATIONS. *Thomas P. Almy, M.D. and John H. Laragh, M.D. (by invitation), New York, New York.*

Reduction of the absolute number of circulating eosinophils following pituitary adrenocorticotrophic hormone (ACTH) has been shown to depend upon the presence of normally functioning adrenal cortices. The adrenal cortex of animals is known to be stimulated by epinephrine, by insulin and by non-specific stress.

In the present work twenty healthy persons given 0.5 cc. of 1:1,000 epinephrine subcutaneously responded with a fall in circulating eosinophils within three hours, averaging 56 per cent of the initial count. In twelve subjects given intravenous insulin (0.1 unit 1 Kg.) the eosinophil count fell an average of 57.5 per cent in four hours. Profound eosinopenia was noted three to eight hours following surgical operations in fourteen of fifteen subjects, the average drop being 85 per cent.

The response to epinephrine or insulin was diminished or absent (average fall 6.8 per cent) in four subjects with adrenal insufficiency and in two patients with hypopituitarism. The response was normal (average fall 55.2 per cent) in six patients with pituitary tumors in which hypopituitarism was absent. The response was exaggerated (average fall 82 per cent) in five patients with essential hypertension.

THE NATURE OF THE COAGULATION DEFECT IN HEMOPHILIA: STUDIES ON PLATELET-FREE PLASMAS. *Robert C. Hartman, M.D., C. Lockard Conley, M.D. and John S. Lalley, M.D. (introduced by George S.*

Mirick, M.D.), Baltimore, Maryland. (From the Division of Clinical Microscopy, Department of Medicine, Johns Hopkins University and Hospital.)

By means of silicone-treated apparatus and high speed centrifugation at low temperatures, platelet-free plasma can be prepared without the use of anticoagulants. This plasma remains fluid at 2°C. for at least several days. Invariably normal platelet-free plasmas clot in a relatively short time when transferred to glass tubes at 37°C., but in silicone-treated tubes the clotting time is greatly prolonged and with perfect technic no clotting at all may occur. On the other hand, hemophilic platelet-free plasmas are spontaneously incoagulable in both glass and silicone-treated tubes at 37°C. No evidence was found for the existence of a clotting inhibitor in the plasmas from the uncomplicated cases of hemophilia studied. The authors concluded that in normal plasma an inactive thromboplastin exists which can be activated by contact with surfaces which can become wet. This factor is apparently deficient in hemophilic plasma. This inactive plasma thromboplastin shows the same physiologic activity and may be identical with the antihemophilic globulin of Patek and Stetson.

THE CLOTTING MECHANISM IN LIVER DISEASE: A PRELIMINARY REPORT. *W. J. Harrington, M.D., C. Crow, M.D., H. Minkel, M.D., J. Desforges, M.D. (by invitation) and R. Manheimer, M.D. (by invitation), Boston, Massachusetts.* (From the 1st and 3rd Medical Services (Tufts) Boston City Hospital.)

It has been observed that in diffuse liver disease a tendency to abnormal bleeding occurs, often unassociated with significant alteration of the prothrombin clotting time. Nor has the clotting time (C.T.) in glass consistently revealed any coagulation defect. This is a report on the investigation of sixty-five patients; studies included clotting times in glass and in silicone-coated tubes and one-stage prothrombin clotting times.

In thirty cases of Laennec cirrhosis twenty-two patients showed prolonged C. T. in silicone while only one was prolonged in glass. In two cases of toxic cirrhosis normal C. T. were found and this was true of two cases of cholangiolitic

hepatitis. In fifteen cases of infectious hepatitis all clotting times were prolonged in silicone and four were prolonged in glass. In four cases of acute obstructive jaundice there were two slightly prolonged C. T. in silicone and none in glass. Of seven cases of chronic obstructive jaundice all had prolonged clotting time in silicone and five were prolonged in glass. In five cases of metastatic cancer to the liver one patient showed a slightly prolonged C. T. in silicone.

There was no relationship between the prolonged clotting time in silicone and the prothrombin clotting time unless prothrombin clotting time was below 30 per cent of normal. In this instance, except in two cases, all the clotting tests in silicone were prolonged.

EVIDENCE THAT DYES USED IN TESTING LIVER FUNCTION ARE REMOVED BY HEPATIC PARENCHYMAL CELLS RATHER THAN BY KUPFFER CELLS. *Albert L. Mendeloff, M.D. (introduced by Kendall Emerson, Jr., M.D., Boston, Massachusetts.* (From the Evans Memorial, Massachusetts Hospitals and the Department of Medicine, Boston University School of Medicine.)

Although certain intravenously administered dyes have been used in the assessment of hepatic function for years, the exact mechanisms by which the liver removes them from the blood are poorly understood. The relative importance of the hepatic parenchymal cells and the Kupffer cells in the removal of the dyes has not yet been ascertained.

The dye rose bengal (tetrachlor-tetraiodo-fluorescein), was found to emit an orange-brown fluorescence in ultraviolet light of wavelengths 3150 to 3650 Ångströms. Tissues stained with 1 to 2 per cent solutions of this dye emitted strong fluorescence which was readily observed by long ultraviolet light through glass condensers, mirror and slides.

Aqueous solutions of the dye (1 to 2 per cent) were administered intravenously to twenty rabbits; liver and splenic biopsies were taken from one to fifteen minutes thereafter. The tissues were immediately frozen and cut in 15 micra sections, floated on water and mounted. The characteristic sustained fluorescence of rose bengal was noted constantly in the hepatic parenchymal cells; no such fluorescence was seen in the Kupffer cells which emitted their

characteristic yellow-green, rapidly fading fluorescence. The fluorescence due to rose bengal was absent or very faint in splenic tissue and apparently when present was located in the sinusoids rather than in the parenchyma.

Since other evidence obtained in this laboratory, in man, shows that the hepatic uptake of rose bengal is slowed or blocked by simultaneously-administered bromsulfalein, it is suggested that normal removal of these dyes from the blood stream is a function of the hepatic parenchymal cells rather than of the Kupffer cells.

DIAGNOSIS OF CARCINOMA OF THE BILIARY TRACT AND PANCREAS BY SMEARS OF EXFOLIATED CELLS IN DUODENAL DRAINAGE. *W. W. Byrnes, M.D., H. M. Lemon, M.D. and G. F. Miller, M.D., (introduced by Kendall Emerson, Jr., M.D.), Boston, Massachusetts.*

The cytology of the duodenal drainage in a series of over thirty-five diagnostic problems has been investigated with a modification of Papanicolaou's method for staining exfoliated cells. The technic of Lyons has been used in the drainage. The series includes twelve patients with carcinoma of the liver, extrahepatic biliary tract, pancreas and stomach, most of which have been verified pathologically. In this small series 90 per cent accuracy has been achieved in providing histologic indications for surgical intervention in cases of cancer of the bile ducts and pancreas. There has been a very good correlation between tumor cytology and the suspected malignant cell clumps in duodenal drainage. It is believed that this method will provide a means of earlier diagnosis of primary and secondary cancers of the liver, bile ducts, ampulla of Vater, and pancreas since even tumors less than 2 cm. in diameter have yielded highly characteristic cytology.

DIAGNOSTIC VALUE OF DIFFERENTIATING BETWEEN MORPHOLOGICALLY IDENTICAL CELLS BY TISSUE CULTURE. *Machteld E. Sano, M.D. and Carmen T. Bello, M.D., Philadelphia, Pennsylvania.* (From the Department of Research Pathology and the Department of Internal Medicine, Temple University Hospital and Medical School.)

The histopathologic study of pleural effusions and lymph nodes is frequently disappointing.

This is especially true in cases in which the clinical diagnosis is obscure and in which cytologic study is the last hope for obtaining a clear cut diagnosis. In the last ten years the study of lymph nodes by tissue culture has shown that cells originating from tissues with similar histopathology and morphology may grow quite differently. The study of pleural effusions also has shown that cells which appear morphologically identical behave differently in a tissue culture. This is especially true of idiopathic effusions of which we present three cases to illustrate our point.

The history of the first patient and the clinical picture suggested metastatic tumor. X-ray of the spine also suggested multiple metastases. Histopathology revealed lymphocytes, monocytes and occasional neutrophils. On tissue culture there was rapid development of giant cells with a granular center and multiple nuclei. There were epithelioid cells and lymphocytes. A diagnosis of tuberculosis was made. The patient died of meningitis and a positive culture of Koch bacilli was obtained from the spinal fluid.

The second case, a sixty-five year old woman, presented fluctuating temperature and pain in the right side of the chest. Cytologic study of the pleural effusion was not revealing. Tissue culture showed rapidly developing cells with bi- and trilobed nuclei. The small lymphocytes showed numerous mitoses. A diagnosis of malignant lymphoma was made, probably a reticulum cell sarcoma with some of the characteristics of a lymphosarcoma. This was confirmed at a later date by biopsy of a lymph node.

In the third case the tentative clinical diagnosis was lung tumor. In tissue culture the lymphocytes, monocytes and occasional neutrophils showed very little activity and rapidly disintegrated. This behavior suggested a regressive process. The patient after thoracentesis recovered rapidly and has been well these last six months.

THE DIAGNOSIS OF ANGINA PECTORIS—A NEW APPROACH. *Herbert R. Brown, Jr., M.D. and Marvin J. Hoffman, M.D. (by invitation), Rochester, New York.* (From the Department of Medicine, University of Rochester School of Medicine and Dentistry and Medical Clinic of The Strong Memorial and Rochester Municipal Hospitals.)

The atypical case of angina pectoris is often missed or confused because of the lack of objective diagnostic criteria. A new approach to more accurate diagnosis correlates elements of history, physical findings, the electrocardiogram when positive and the ballistocardiogram.

The patients were divided as follows into four groups based upon symptomatology: (1) typical cases of angina pectoris without a history of coronary failure or coronary occlusion, (2) typical cases of angina pectoris with a history of coronary failure, (3) coronary thrombosis with myocardial infarction and (4) the atypical cases in which ascertaining the presence or absence of coronary artery disease is at present done with considerable uncertainty.

The most significant positive factor in this series was the establishment of a correlation between the definite cases of angina pectoris and abnormal ballistocardiographic tracings. The first ballistocardiographic evidence of abnormality is an increased respiratory variation brought about by a decreased amplitude during expiration. This probably results from a decreased venous return. Further abnormalities are indicated by the presence of irregularity, lack of definition and decreased amplitude throughout all of the wave patterns. The cases of coronary failure and myocardial infarction revealed through the ballistocardiogram a more severe degree of impairment. This relationship was next used to detect the presence or absence of coronary artery disease in atypical cases. This approach represents a means of diagnosing angina pectoris, typical or atypical, with a consistency heretofore unobtainable.

EFFECT OF EPINEPHRINE, AMINOPHYLLINE AND DIGITOXIN ON THE OXYGEN CONSUMPTION OF RABBIT HEART SLICES.
Leon Levinson, M.D. and Mark Aisner, M.D., Boston, Massachusetts. (From the Departments of Physiology and Medicine, Tufts College Medical School.)

Vasopressor substances have generally been regarded as contraindicated in the shock-like state following myocardial infarction. Such substances are believed to cause an increase in the oxygen consumption of the myocardium proportionally greater than the accompanying increase in contractile force, and thus to endanger the tissue in the hypoxic border of the infarct. Digitalis is also generally withheld from

patients with recent myocardial infarcts for similar reasons. Aminophylline, on the other hand, is often given freely although evidence has been presented indicating that this drug may also increase the work of the heart.

Slices of rabbit heart were suspended in a glucose-containing modified phosphate-buffered Ringer's solution and oxygen consumption determined by the Warburg technic. No statistically significant effect upon oxygen consumption occurred when epinephrine ($1 \text{ by } 10^{-5}$ and $1 \text{ by } 10^{-7}$), digitoxin ($2 \text{ by } 10^{-5}$ and $2 \text{ by } 10^{-7}$) or aminophylline ($1 \text{ by } 10^{-4}$) was added. The lower concentrations employed approximate clinical dosage.

The oxidative metabolic mechanism of non-contracting heart muscle is thus unaffected by these drugs. These substances, however, have definite effects on the metabolism of contracting muscle as measured in the Gold papillary muscle preparation. In the dog ligation of a coronary artery leads to immediate cessation of contraction of the involved area. So far as non-contracting tissue is concerned administration of epinephrine, aminophylline or digitoxin has no apparent effect.

MYOCARDIAL LACTATE AND PYRUVATE METABOLISM STUDIED IN NORMAL AND HYPERGLYCEMIC INTACT DOGS BY CORONARY SINUS CATHETERIZATION. *Walter T. Goodale, M.D., Donald B. Hackel, M.D., Martin Lubin, M.D. and Pauline P. Wilson, M.D. (introduced by Kendall Emerson, Jr., M.D.), Edgewood Arsenal, Maryland.* (From the Medical Division, Army Chemical Center.)

Preferential utilization of lactate and pyruvate by heart muscle has been demonstrated but never under normal physiologic conditions. Development of a technic of catheterizing the coronary sinus under fluoroscopic control, however, has made it possible to study myocardial metabolism in both nembutalized and unanesthetized intact dogs.

Coronary arteriovenous differences were estimated from blood samples drawn simultaneously from femoral artery and coronary sinus. Coronary blood flows were measured by the nitrous oxide method. Total myocardial utilization was the product of two independent variables: (1) coronary blood flow and (2) coronary arteriovenous difference. In normals,

coronary arteriovenous lactate and pyruvate differences were, in turn, closely and directly correlated with the respective arterial blood levels.

The mean myocardial lactate utilization was 7.5 mg. per 100 Gm. of heart muscle per minute, and pyruvate utilization was 1.1 mg., with a mean myocardial oxygen consumption of 12 cc./100 Gm./min. Assuming complete oxidation of lactate and pyruvate in the heart, the amounts removed could together account for anything up to 80 per cent of the current myocardial oxygen consumption, this percentage depending in the normal almost entirely upon the arterial levels of each metabolite. No myocardial glucose utilization was demonstrable and no ketone body utilization was found at normal levels. In hyperglycemia from glucose infusion, lactate and pyruvate blood levels rose but with the same myocardial lactate and pyruvate utilization compared to their arterial levels as was found in normals.

Lactate and pyruvate thus appear to be preferred sources of energy for the myocardium and are increasingly utilized as their arterial levels and the coronary blood flow rise. Glucose, even when present in excess, apparently does not compete with lactate or pyruvate for myocardial utilization. These facts may help to explain logically the excellent adaptation of the heart to stress or to the increased work of severe exercise.

ELECTROLYTE CHANGES IN CONGESTIVE HEART FAILURE: EFFECTS OF ADMINISTRATION OF POTASSIUM AND SODIUM SALTS. Charles L. Fox, Jr., M.D., Charles K. Friedberg, M.D. and Abraham G. White, M.D. (by invitation), New York, New York. (From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University and the Medical Service, Mt. Sinai Hospital.)

The electrolyte pattern of the plasma, edema fluid and urine during acute congestive heart failure and after recovery was investigated together with the effects of administering various mixtures of potassium and sodium salts.

With chronic congestive heart failure, the plasma sodium was subnormal (112 to 132 mEq. per L.) in nineteen patients; two patients had high values (148 and 150); five patients ranged from 133 to 142. Plasma chlorides did not

parallel sodium; they were reduced in nine patients (93 to 101 mEq. per L.) and elevated in twelve patients (106 to 112 mEq. per L.) with four in the normal range (101 to 106 mEq. per L.). Plasma potassium was subnormal in ten (2.3 to 3.5), above normal in three (5.4, 5.8 and 7.3) and normal (4 to 5) in six. After recovery from failure measurements were repeated in five patients and plasma sodium increased from 4 to 15 mEq.; plasma potassium when subnormal also increased (3.0 and 3.2 going to 5.0 and 5.2, respectively).

After injection of a mercurial diuretic but before the onset of diuresis, changes in the electrolyte composition of the edema fluid were observed. With diuresis, marked changes in the electrolyte pattern of the urine resulted. The administration of NaCl or KCl resulted in positive chloride balances and weight gain. When these cations were given with organic anions, little or no weight gain occurred despite the markedly positive sodium balance. Simultaneous administration of K acetate and NaCl diminished the weight gain and positive chloride balance.

In these studies gain or loss of weight did not appear to be a simple function of sodium balance. The observations suggest that intracellular and extracellular ionic relationships may play a part in the phenomena of congestive heart failure.

LIFE SITUATIONS, EMOTIONS AND HUMAN COLONIC FUNCTION. William J. Grace, M.D., Stewart Wolf, M.D. and Harold G. Wolff, M.D. (by invitation), New York, New York. (From the Departments of Medicine and Psychiatry of the New York Hospital and Cornell University Medical College.)

We have had a unique opportunity to study the behavior of the human colon in two fistulous subjects, with particular emphasis on the influence of emotions and feeling states. Subject A had a large prolapse of the ascending colon and cecum through a cecostomy wound. Subject B had a large prolapse of the descending colon and sigmoid through a colostomy incision.

Our findings indicate that situations productive of anger, guilt, resentment and hostility are accompanied by hyperfunction of the large bowel. This hyperfunction is manifested by an increase in motor activity, blood flow,

lysozyme production and usually mucus secretion. In severe induced pain under experimental circumstances there was intense fear and fright and a pallor and relaxation of the large intestine. Increase in motor activity, blood flow and secretion of the large bowel occurred regularly following ingestion of an average meal. However, in one of our subjects little change in activity was noted when he was in a period of low spirits, dejection and mild depression. Other threats to bodily and personal integrity, such as sigmoidoscopic examination, personality study and having the patient perform a psychometric test, resulted in an increase in motor activity and blood flow. A period of sustained anger, resentment and hostility resulted in a profuse eruption of petechiae throughout the surface of the exposed colon.

COMPARATIVE STUDY OF THE EFFECTS OF MILK AND HYDROLYZED PROTEIN ON GASTRIC AND DUODENAL BULB ACTIVITY IN DUODENAL ULCER. *Mieczyslaw S. Lopusniak, M.D. (introduced by Irwin J. Pincus, M.D.), Philadelphia, Pennsylvania.* (From the Graduate Hospital of the University of Pennsylvania.)

The studies on which this report are based were undertaken: (1) to observe the effects of an aqueous mixture of casein hydrolysate, dextrins and maltose on the acidity of the contents of both the duodenal bulb and pars pylorica in patients with active duodenal ulcer and (2) to compare these effects with those of milk and a mixture of milk and cream. Eleven patients with clinical and roentgenologic evidence of active duodenal ulcer were selected for study. The amount of each foodstuff and the frequency of administration were so chosen as to duplicate clinical methods of treating ulcers which utilize these substances. Material was extracted by means of a special double-lumen tube from either side of the pylorus before and at intervals after the feeding of each of the substances under investigation.

It was found that casein hydrolysate more effectively buffered and neutralized gastric and duodenal bulb acidity over a two-hour period than did an equal quantity of milk or a mixture

of milk and cream fed hourly over the same period. Under the experimental circumstances of the study and on the basis of the criteria used the hydrolyzed protein mixture employed was, nevertheless, an imperfect buffer and neutralizer of gastric and duodenal bulb acidity in these duodenal ulcer patients. Fairly marked secondary stimulation of active secretion in the stomach regularly followed its ingestion.

STUDIES IN PULMONARY FUNCTION BEFORE AND AFTER PULMONARY RESECTION FOR BRONCHIECTASIS AND OTHER PULMONARY DISEASE. *Joan H. Long, M.D., W. Emory Burnett, M.D., Charles M. Norris, M.D. and M. R. Wester, M.S. (introduced by Thomas M. Durant, M.D.), Philadelphia, Pennsylvania.*

By means of external spirometry and bronchspirometry, changes in the volume of air moved and in oxygen absorption after the surgical removal of one or more pulmonary segments have been studied in sixty-four patients with bronchiectasis and in five patients with other pulmonary disease. Studies were done preoperatively two weeks postoperatively and again six months to two years later.

It was found that in unilateral bronchiectasis the oxygen absorption is reduced more than the volume of air moved on the affected side. The maximum breathing capacity during voluntary effort is reduced in a manner roughly proportional to the extent of the disease. This decrease is due in most instances to a decrease in the depth of respiration during this effort. After the resection of one or more pulmonary segments the voluntary maximum breathing capacity may be increased.

Only occasionally is there an increase in the percentage of the total air moved by the remaining lung segment on the operated side; usually there is no change or a decrease of the percentage of air moved by that side. On the other hand, it is a little more common to find an increase in the percentage of the total oxygen absorbed by the remaining lung segment on the operated side although, again, in the majority of cases there is either no change or a decrease in this function.

Case Reports

Fulminating Fatal Gout*

H. SPITZ, M.D., O. STEINBROCKER, M.D. S. SCHWARTZ and M. SCHITTONE, M.D.

New York, New York

RECENT reports¹⁻³ have tried to focus the interest of the medical practitioner on articular gout again since it is all too often neglected in the differential diagnosis of acute and chronic joint diseases. Gout is much more common than is generally suspected. Although it is apt to become a chronic disease, severe disabling changes are rare. The comparatively few reports of cases in which extensive crippling deformities developed with ankylosis and marked limitation of motion invariably describe a long protracted course of the disease.³⁻¹⁰ Rapid progression of the disease to a crippling stage in the course of only three years is therefore unusual, particularly when the first symptoms do not appear until the fifth decade of life. Such a case was observed with postmortem examination on the wards of Bellevue Hospital and is herewith reported. Another remarkable feature in this case was the association of severe gout with anemia, splenomegaly and sclerosis of the portal vein.

Occasional case reports have appeared describing gout accompanied by various blood dyscrasias such as pernicious anemia,^{11,12} hemolytic jaundice,^{10,13,14} erythronoclastic anemia¹⁵ and anemia of undetermined type.¹⁶ In several instances splenomegaly with anemia are described without further remarks about the type of the anemia.^{6,17,18} No mention, however, is made in these reports of the appearance of the portal vein. Therefore, it seems that this is the first reported case showing sclerosis and calcification of the portal vein and its main tributaries associated with "splenic anemia" and gout.

CASE REPORT

C. L., a forty-seven year old, unmarried Chinese male who worked as a waiter, was admitted to the hospital on September 12, 1944, with chief complaints of pain in all his limbs (knees, feet, wrists, hands and elbows). He had felt well until three years before when he experienced a sudden pain in his big right toe followed by pain in his legs and arms. Simultaneously, small lumps appeared on his hands and about his joints. The lumps enlarged progressively, became more numerous and were tender to pressure. Pain in his extremities gradually became more severe. For the two years before admission he was unable to work. The pain was lancinating and almost continuous just before admission. Anorexia had been present for two months, with resulting marked weight loss. He had difficulty in retaining urine; the systemic review was otherwise negative.

Examination on admission revealed a cachectic, restless Chinese in acute pain. His temperature was 100°F., pulse 80, respiration 30 and blood pressure 146/76. The head, eyes, ears, nose, throat and lungs were normal. His heart was greatly enlarged to the left. Over the precordium a loud, blowing, systolic murmur was heard. The rhythm was regular. The liver edge was said by some examiners to be sharp and 2 cm. below the right costal margin. The lower pole of the spleen was found to be about 8 cm. below the left costal margin, smooth, non-tender and ballotable because of the presence of peritoneal fluid. There was no abdominal tenderness or rigidity. The kidneys were not felt. The prostate was hard, nodular and slightly enlarged.

There was hyperkeratinization of the skin, most noticeable over the waistline, legs and feet, with ulceration, crusting and painful edema of the feet, particularly of the dorsal surfaces. Numerous freely movable, subcutaneous nodules were felt in the thighs, around the elbows and

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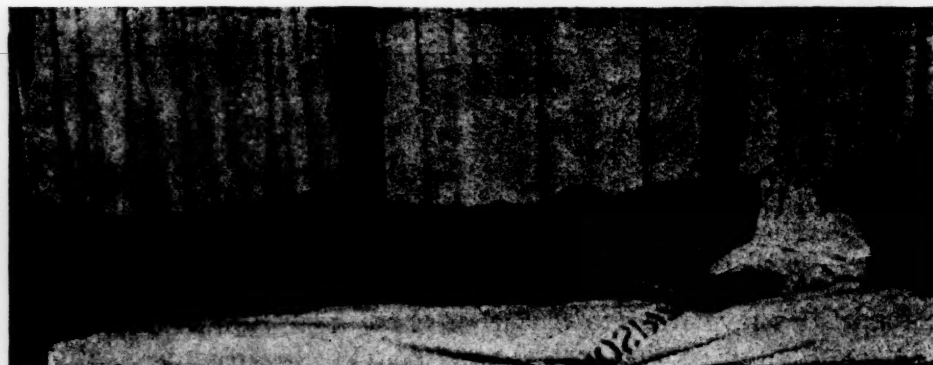


FIG. 1. Nodules over the knees and hands; cachexia.

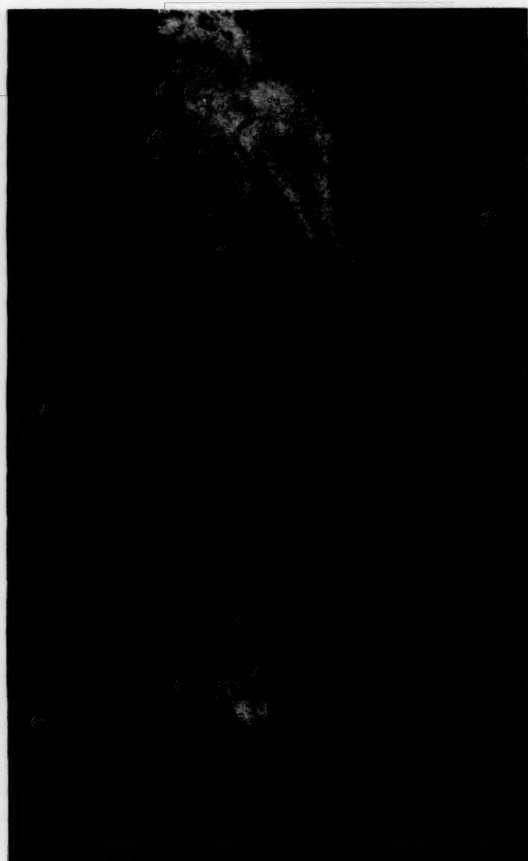


FIG. 2. X-ray of the right hand. There are no definite punctate erosions despite destructive changes in the middle phalanx of the middle finger where a subcutaneous and an osseous tophus were present with fistula formation. The lesion in the fifth metacarpal bone was interpreted as chondroma.

knees and along the fingers. (Fig. 1.) All of these were tender and in addition some were fluctuant. The hard nodules had a yellowish tint and the veins nearby were distended and surrounded with small hemorrhages. One of the nodules on the right middle finger had broken

down and was discharging cheesy, gritty material containing needle-like crystals. The extremities were wasted and had flexion deformities.

Laboratory data on admission revealed a white blood count of 10,000 with 82 per cent polymorphonuclears and 18 per cent lymphocytes; red blood cells, 1.7 million and hemoglobin 4.5 Gm. Blood Wassermann and Kahn tests were negative. The urine was acid, its specific gravity was 1.014. It contained no albumin, glucose or pathologic microscopic sediment. The blood non-protein nitrogen was 31 mg per cent; uric acid on whole blood, 7.7 mg. per cent; serum calcium 9.1 mg. per cent; phosphorus 3.9 mg. per cent. The cephalin flocculation test was strongly positive; albumin globulin ratio 3.1/4.5; alkaline phosphatase 21.1 Bodansky units; total cholesterol 105 mg. per cent and esters 49 mg. per cent.

The icteric index was 5 on September 13th and rose to 18 on September 20th when a direct, immediate Van den Bergh reaction was obtained. Stool examination for parasites was negative. The electrocardiogram did not reveal any abnormality. X-ray of the chest showed a moderate increase in the size of the heart, with diffuse engorgement in both lungs. In both knee joints hypertrophic changes were found. An expansion of the shaft of the fifth metacarpal bone was interpreted as chondroma. (Fig. 2.) The proximal phalanx of the third right finger showed evidence of periostitis. (Fig. 2.) There was periarticular soft tissue swelling of the right ankle joint. Osteo-arthritic changes were noted in the tarsal bones.

The patient ran an irregular febrile course with occasional rises of temperature to 103°F. On the seventh hospital day a transfusion of 500 cc. of whole blood was given without incident. Immediately following this procedure the temperature dropped to normal and remained

so. The patient was treated with full doses of colchicine and aspirin and with large amounts of multiple vitamins and iron without subjective or objective improvement. His condition deteriorated rapidly until his death on the twenty-seventh hospital day.

Autopsy was performed eight days after death. It revealed an emaciated Chinese male of slender body build appearing somewhat older than the stated age of forty-seven. There was no peripheral edema. No icterus of the sclerae was noted. The superficial lymph nodes were not enlarged. The skin was dry, inelastic and scaly. The feet and hands were covered with numerous subcutaneous nodules varying in diameter from 0.5 to over 3 cm. The nodules were most numerous over the extensor and flexor surfaces of the metacarpophalangeal joints. They were present to a lesser extent over the shafts of the phalanges, metacarpal bones, wrist, elbow, ankle and knee joints. Nodules also were present along the long bones of the upper and lower extremities. No tophi were found in the earlobes. Many of the nodules were attached to the underlying structures but not to the skin. Some were soft and fluctuant while others were firm. One nodule on the dorsal aspect of the right middle finger had ulcerated through the skin and white chalk-like, gritty material could be expressed. Smears of this material showed characteristic sheaves of doubly refractive urate crystals. The ankles and dorsal aspects of the feet were slightly swollen. The overlying skin was superficially excoriated and stained violet (gentian violet). The joints of the fingers and toes showed marked decrease of passive mobility although rigor mortis had completely subsided. Bony hard excrescences were felt along the joint lines of the knees, elbows and wrists. An incision over the dorsum of the left hand exposed numerous tophi on the extensor and flexor surfaces of the hand. The nodules involved tendon sheaths and ligaments and widely replaced the muscles of the palm. Some of the nodules were composed of opaque, gritty material and others contained pale green pus. The first metacarpophalangeal joint was opened. The exposed cartilage was smooth of surface but thinner than normal, opaque and chalky white. Longitudinal section of the metacarpal bone showed minute opaque deposits between the trabeculae of cancellous bone in the metacarpal head and erosion of the metaphyseal compacta by tophi.

The pleural cavities contained small amounts

of clear fluid. The peritoneal cavity contained no excess fluid; the heart weighed 340 Gm.; its chambers were slightly dilated and the left ventricle measured up to 23 mm. in thickness. The coronary arteries were thin-walled and patent throughout. The aorta was narrow, elastic and showed no atherosclerotic changes. The lungs were congested and edematous posteriorly. The liver weighed 1,200 Gm. It was firm and covered by a thin translucent capsule. On section the lobular architecture was accentuated by congestion of the central veins. The left lobe of the liver was thin, flabby and appeared atrophic. The intrahepatic branches of the portal vein and all its main roots were dilated and lined by thick opaque intima. In the portal vein and in the adjacent portion of the splenic vein fibrous ridges projected about 1 mm. above the intimal surface criss-crossing in all directions. Between these ridges the vascular wall was thinner and bulged outward. The deepest pouch was situated on the anterior surface of the portal vein. It was 6 mm. deep and filled with firmly adherent yellow to dark red thrombotic material. Similar thrombi were present in the splenic vein close to its junction with the superior mesenteric vein, causing only slight stenosis of the lumen. Plaques of lime salt deposits were present in the portal and splenic veins between the aneurysmal bulges. The remainder of the splenic vein was tortuous and dilated averaging 4 cm. in circumference. The proximal portion of the superior mesenteric vein was 3 cm. in circumference and its smaller branches were dilated, tortuous and slightly sclerosed. The spleen was considerably enlarged and weighed 530 Gm. The capsule was thick, opaque, covered with hyaline plaques and adherent to the diaphragm. Cut surface was dry, flat, pink to red and traversed by numerous prominent trabeculae forming narrow spaces filled with firm pulp.

Gallbladder, adrenals and pelvic organs showed no important changes. There were no biliary calculi present.

The kidneys were of average size and each weighed 115 Gm. The capsules could be stripped with moderate difficulty revealing smooth surfaces. The left kidney was dark red with a few small yellow areas over the lower pole. Several small cortical cysts were present. The cortex averaged 4 mm. in width and showed the usual striations. The pyramids were congested and streaked white by gritty and granular deposits. Scattered through the cortex and pyramids were

multiple abscesses measuring 1 to 2 cm. in diameter. The right kidney was similar but generally paler. Renal pelves and ureters showed no abnormality. No renal calculi were found.

The neck organs were not unusual. The vertebral column and the bones of the thoracic cage appeared unaltered and contained abundant dark red marrow. The external iliac lymph nodes were enlarged and soft. The cerebral arteries showed no arteriosclerosis.

Histologically, section of the heart showed mild hypertrophy and occasional basophilic degeneration of the myocardial fibers. Precipitated edema fluid was present in the alveoli in the posterior portions of the lungs. Sections from the right lobe of the liver revealed only mild congestion. In the left lobe dilated bile ducts were found surrounded by broad sheaths of fibrous tissue enclosing many small bile ducts and small scattered groups of liver cells. Neighboring liver lobules presented a normal appearance. No evidence of recent degeneration or necrosis of liver cells was found. The portal vein showed extensive changes in its wall. Intima and media were replaced by sclerosed fibrous tissue, irregularly intermingled with elastic lamellae. The fibrous tissue wall was fused with a laminated, hyalinized thrombus. In the adventitia thick bundles of smooth muscle were found arranged longitudinally along part of the circumference.

Sections of the spleen showed considerable thickening of the capsule and trabeculae by compact fibrous tissue. The malpighian corpuscles were few in number and the ones that remained were small and indistinct. The sinuses were empty, dilated and lined by prominent hyperplastic endothelium. The pulp was poor in cells and slightly fibrosed.

Sections of the kidney revealed several minute, narrow wedge-shaped, subcapsular scars with atrophy of the tubules, hyalinization of the glomeruli and interstitial fibrosis. Some of the atrophic tubules contained hyaline casts. The majority of the glomeruli were well preserved. The tubules were slightly dilated and contained a finely granular precipitate. The lining cells presented considerable postmortem changes. A few cortical cysts were lined by low cuboidal epithelium. The arterioles showed minimal thickening of the intima. Small and medium-sized arteries were of average caliber and their intima was slightly thickened by fibrous tissue. Scattered through pyramids and occasionally

extending into the inner half of the cortex were round or oval areas composed of a finely granular or fibrillar pale staining acidophilic material. (Fig. 3.) Small, irregular, empty spaces in this material indicated the presence of lipids and the acidophilic material often showed a radial star-like streaking. In some of these foci rhomboid, highly refractive and doubly refractive, pale yellow crystals were found lying singly, in irregular clusters or in sheaves. (Fig. 3.) Foreign body giant cells were attached to some of these crystals and surrounded smaller ones completely. At the periphery of these crystalline deposits a scant infiltrate of mononuclear cells was found. Mononuclears in radial arrangement also seemed to interdigitate with the radial striations previously mentioned.

Furthermore, focal abscesses were found in the parenchyma; some of them contained crystalline deposits and all of them were surrounded by an acute inflammatory reaction. Casts of polymorphonuclears were present in collecting tubules in these areas. A calyx showed severe inflammatory reaction; the surface epithelium was desquamated and loose and was mixed with polymorphonuclears and urate crystals. The mucosa was markedly congested and infiltrated with polymorphonuclear leukocytes and lymphocytes. Some kidney sections were stained according to the method of De Galantha.²⁹ (Fig. 4.) A starfish-like arrangement of black threads was thus revealed in the granular matrix previously described. Control stains for argyrophilic reticulum failed to demonstrate these structures, indicating that they were not reticulum fibers but urate crystals.

Section through the head of a metacarpal bone and the surrounding soft tissues (Figs. 5 and 6) revealed urate deposits in the articular cartilage, the cancellous bone of the capitulum and the metaphysis and in the periarticular structures. The surface of the hyaline cartilage was irregular, frayed and covered by granulation tissue (pannus) near the articular margins. Occasional deep fissures penetrated almost the entire thickness of the cartilage. Scattered through the hyaline cartilage were clusters of pale yellow, doubly refractive crystalline plates usually rhomboid in outline with longitudinal striations. Occasionally these crystals showed an arborescent arrangement. They lay close to the articular surface but were usually separated from it by a thin rim of apparently unaltered cartilage. The hyaline cartilage around these

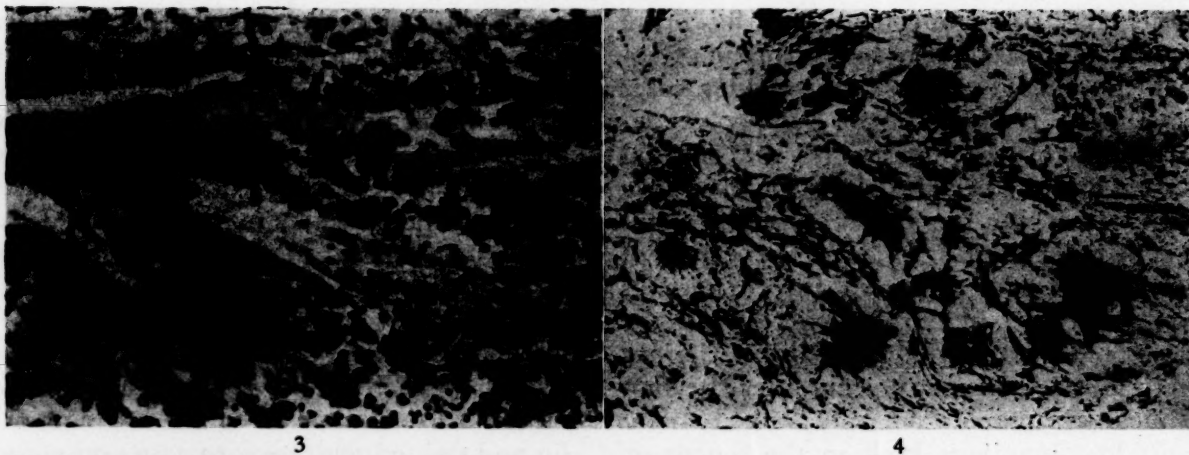


FIG. 3. A, water-soluble and B, water-insoluble urate crystals in the kidney. ($\times 552$.)

FIG. 4. Water-soluble urate crystals in the kidney stained black according to the method of E. De Galantha. ($\times 144$.)



FIG. 5. Longitudinal section through the head of the metacarpal bone shows tophi in the periarticular connective tissue (A), and urate deposits in the articular cartilage (B), and in the bone marrow (C).

FIG. 6. Urate deposits in the articular cartilage. ($\times 144$.)

deposits showed no evidence of necrosis. The pannus covering the cartilage was also encrusted with urate deposits. On the volar aspect of the metacarpal head the cartilage was undermined by urate deposits which extended from large tophi in the capsular ligaments and the periarticular fibrous connective tissue. At one point the pannus bridged the articular space and attached the two opposing articular surfaces to each other. The osteocartilaginous border was sharp everywhere. The fibro-fatty marrow in the head and the distal metaphysis of the metacarpal bone contained urate deposits indicated by the eosinophilic matrix as seen in the kidneys. The crystals proper had apparently been dissolved and could not be seen in these sections that had been fixed in Zenker's solution and embedded in paraffin. Water-insoluble crystals were also present and were similar to those seen in the articular cartilage and in the kidneys.

In the periarticular tissue on the volar and dorsal aspects of the bone there were large tophi surrounded by fibrous tissue capsules. In these capsules and around small globules of urate deposits many foreign body giant cells and occasional large mononuclears could be seen. The smaller globules were composed principally of eosinophilic, granular or amorphous material, the matrix of soluble urate crystals. Small arteries and arterioles in the fibrous tissue around the joint showed mild to moderate fibrous intimal thickening.

The vertebral bodies contained highly cellular marrow, showing a slight preponderance of the erythropoietic elements. The bony trabeculae were unaltered. No urate deposits were present.

COMMENTS

Several features of this case warrant comment. One is the extensive involvement of

joints and subcutaneous tissues by urate deposits and secondary hypertrophic osteoarthritic changes. Occasional similar cases have been reported.^{3-10,19} Exhaustive descriptions of the lesions in the skeletal system and the periarticular structures have appeared in the literature; especially Pommer's description^{20,21} gives an excellent account of such morphologic changes as were observed in our patient. In all the cases reported extreme disabling lesions were found only many years after the first clinical symptoms had appeared. Usually gout first manifests itself in the fourth or fifth decade. Acute attacks of gouty arthritis are followed by complete remissions. During such remissions the patients feel perfectly well and in the beginning are able to carry on their usual occupation. Much later slight disability persists throughout the interval between attacks and after many years, sometimes ten, sometimes twenty or more, the joint lesions lead to complete invalidism. If the first attack occurs early in life, the articular lesions usually are more severe. It is therefore remarkable that although the patient experienced his first attack of joint pain at the age of forty-four the disease took such a devastating, rapidly progressive course and produced such extensive, crippling joint lesions in the comparatively short period of three years. Contrary to older concepts, gout is not uncommon in poorly nourished individuals who do not indulge in excessive food or alcohol intake.³ This patient showed no evidence and gave no history of antecedent overeating or obesity. Gout supposedly affects Orientals much less frequently than Europeans.²² Snapper does not even mention gout in his monograph on Chinese medicine.²³ Scattered reports of gout in Chinese, however, show that this race is not exempt.^{7,22,24}

Another remarkable feature was found in the morphology of the urate crystals since there were obviously two types of crystalline deposits in the tophi in cartilage, bones and kidneys. One type occurred in fine needles, usually in radial arrangement deposited in an acellular, finely granular or amorphous

eosinophilic matrix. Foreign body giant cells, lymphocytes and fibroblasts were found around these crystals. In preparations fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin the crystals had disappeared and only their molds in the granular matrix remained. In order to demonstrate the crystals, fixation in absolute alcohol and staining according to the method described by De Galantha²⁵ were used. There were in addition other crystals which were plainly visible in formalin-fixed material, embedded in paraffin and stained with hematoxylin and eosin. They were, therefore, insoluble in water, alcohol and xylol; and since they also appeared in sections of bone decalcified with sodium citrate and formic acid, they were insoluble in weak acids. They were rhomboid in outline, doubly refractive, showed longitudinal striations and occurred in irregular clusters or sheaves of elongated blunt needles. Only one reference to these crystals was found in the literature.⁵ There it was suggested that the more recent urate deposits are water-soluble and the older deposits water-insoluble. Many of the standard textbooks on clinical pathology do not mention the morphologic detail and the physicochemical properties of these crystals at all or describe only one type.

The renal lesions were of particular interest since there was no clinical evidence of impaired renal function. Arteriolar nephrosclerosis and hypertension are considered common complications of gout.^{3,16} They were almost entirely absent in our patient. Only mild sclerosis of a few arterioles and small arteries was present and corresponding minute subcapsular scars were found. Although many observers believe that arteriosclerosis and nephrosclerosis are more common and appear earlier in gouty patients than in non-gouty people in comparable age groups,²⁶ the vascular changes and especially signs of renal failure appear late in the disease; however, a causal relationship of gout, nephrosclerosis and hypertension is by no means universally accepted.

Schnitker²⁶ claims that almost all gouty patients who die before the age of fifty and a significant percentage of those in the older age groups succumb because of this renal complication. Renal function tests on patients suffering from gout led Talbott³ to believe that the majority of patients with gout, irrespective of age or duration of symptoms, have impairment of renal function. The anatomic changes in the kidneys are usually those of vascular nephrosclerosis although they have been called vascular nephritis, chronic interstitial nephritis or gouty kidney—terms that should not be employed. Actually the lesions are indistinguishable from arterial and arteriolar nephrosclerosis as seen in benign hypertension. Occasionally chronic glomerulonephritis was found.¹⁰ The pathogenesis of the renal lesions is a matter of much dispute. They are attributed to the deposition of urates in the renal tubules and parenchyma by some,³ whereas others claim that the urate deposits can exist in the gouty kidney without manifestation of chronic nephritis and that they have in no way any causal relationship to the renal disease.²⁷ Observations in our patient tend to support at least the first half of the preceding statement. The concept of a higher incidence of arteriosclerosis and hypertension in gout than in a comparable group of people without gout is also not accepted by all observers. It is believed by some French authors especially that arteriosclerosis and gout do not have a cause and effect relationship but are rather the result of a disturbance of nutrition leading to gout and to arteriosclerosis.^{28,29} These authors even claim that arteriosclerosis and hypertension occur in the same percentage in gouty and non-gouty persons in the same critical age group, a statement that is diametrically opposed to the view held by Schnitker.²⁶ Thus, the French authors consider as highly exaggerated the opinion of those who like Huchard maintain that "gout is for the arteries what rheumatic fever is for the heart." But even if one accepts Schnitker's figures and the studies by Talbott³ and

others³⁰ on renal function in patients with gout, it does not necessarily follow that the deposits of urates in the kidney are the cause for extensive vascular sclerosis and renal damage. No detailed studies of renal function were attempted in our case, but routine urine and blood examinations did not suggest appreciable renal damage and still there were numerous urate deposits scattered through the renal parenchyma. It is conceivable that the total duration of the illness was too short for nephrosclerosis to develop. The deposition of urates in the kidneys *per se* did not lead to appreciable renal damage and in the course of several years development of hypertension and nephrosclerosis would not necessarily have to be interpreted as caused by gout. It should be remembered that gout is a hereditary constitutional disorder and that arteriosclerosis also is considered by some to have a hereditary or familial background.

Interstitial urate deposits in the kidney are usually not associated with severe inflammatory reaction. This patient, however, presented considerable acute and subacute pyelonephritis with abscess formation limited to the areas that contained the crystalline deposits. On the other hand, not all urate deposits were surrounded by abscesses or any other extensive inflammatory reaction. It may be assumed that the stagnation—an important factor in the development of pyelonephritis—was not uniform throughout the kidney. This is suggested by the presence of cellular debris mixed with polymorphonuclear leukocytes and urate crystals in some calyces and not in others.

The roentgenologic findings were not characteristic of gout.³¹ X-rays showed no specific changes as reported in the literature.^{3,4,6,15,19} In addition to periarticular soft tissue swelling, there were hypertrophic changes in the knee joints and tarsal bones.

Clinically, there was definite evidence of impaired liver function. No anatomic changes were found that would adequately explain this. The atrophy of the left lobe of the liver appeared to be old and involved too little liver parenchyma to cause a

clinically detectable change in liver function. Enlargement of the liver with tenderness and jaundice is occasionally present in gout.²² The enlargement is usually due to fatty change and chronic passive congestion. No fatty change was present in our patient nor was there appreciable congestion. No explanation can be given for this discrepancy.

The association of gout with splenomegaly and anemia deserves particular comment. Few similar cases have been reported.^{6,10,15,17,32} They present in most instances a fortuitous coincidence of gout and splenic anemia. Gout may appear sometimes during the course of pre-existing anemia with splenomegaly¹⁰ or the latter may intervene during the course of chronic gout.¹⁷ A complete autopsy was performed in only three of the cases reported. In two of them congenital hemolytic anemia was the associated disease¹⁰ and in the third the exact nature of the anemia and splenomegaly is not clear.⁶ Phlebosclerosis with calcification of the portal vein and its main tributaries with thrombosis, splenomegaly and anemia is not described in these reports. Phlebosclerosis of the portal vein has been the subject of many case reports.³³⁻³⁵ The lesion may be produced by a variety of causes or no cause at all may be apparent.³⁶ X-ray diagnosis of this condition was first described by Moberg.³⁷ In his case calcification had occurred in the thrombus rather than in the vessel wall. The association of gout with calcification of the portal vein might suggest that deposition of urates in the vessel wall had produced necrosis followed by lime salt incrustation. Urate deposits have been found at times in the most unusual locations such as the mitral valve.³⁸ However, we were unable to demonstrate urate crystals or their molds in the wall of the portal vein or its main tributaries. The etiology and pathogenesis of portal vein sclerosis and calcification remain obscure in this case. Discussion of splenic anemia in connection with portal vein sclerosis would go far beyond the

scope of this report and may be found in the relevant literature.

An interesting concept about the possible relationship between anemia and gout was suggested by Krafka.³⁹ He points out that any condition raising the maturation rate of red blood cells leads to increased uric acid output because more nuclei of immature red blood cells are extruded and metabolized. This rise in uric acid output was observed by Krafka in the course of experiments on dogs and by others^{11,12,40} in pernicious anemia during remission, spontaneous or induced. Krafka explains the association of lead poisoning and gout also on the basis of the anemia that is a constant feature of plumbism. He even attributes the disappearance of old fashioned gout of one hundred years ago to the discontinuance of the medical practice of bleeding since even small hemorrhages are marked hemopoietic stimuli. He also mentions one of Garrod's cases,¹⁶ a girl of ten who had her first attack of gout at the age of seven when she was suffering from anemia. It is conceivable that in our case the sclerosis of the portal vein, splenomegaly and anemia preceded the clinical manifestations of gout and that anemia was a precipitating factor. Anemia may provoke attacks of gouty arthritis, but it certainly is not the main etiologic factor since only few people suffering from anemia develop clinical gout. Gout must be considered as a disease developing on a constitutional hereditary basis in which anemia among other disturbances may precipitate the appearance of clinical symptoms.

SUMMARY

1. An unusual case of fulminating gout which occurred in a middle-aged Chinese male is reported. It was of remarkably short duration and exceptional severity, associated with phlebosclerosis, calcification and thrombosis of the portal vein, splenomegaly and anemia.

2. The unusual clinical and anatomic features of the gouty lesions are discussed.

3. The occurrence in the tophi of two types of urate crystals is described.

4. The extent and character of renal lesions are emphasized in the absence of clinical evidence of renal failure.

5. The association of gout and splenic anemia is discussed and reference is made to similar cases reported in the literature.

6. Suggestions in other reports about the possible relationship of anemia and gout are reviewed.

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Friedländer's Bacillus Meningitis Treated with Streptomycin*

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WHILE meningitis due to Friedländer's bacillus was first described some sixty years ago,¹ this disease still remains a clinical rarity. Ransmeier and Major,¹ after a careful survey of the literature up to 1943, could find only twenty-nine cases reported. They added another case. Since that time, twenty-three additional cases^{2-6,11-13,15} have been reported, only nine of them in detail. These cases include meningitis due to *Aerobacter aerogenes*, an organism which appears to be practically indistinguishable from Friedländer's bacillus.

The relative rareness of meningitis due to this group of organisms and the present meager experience with streptomycin treatment prompt the present report of a case of meningitis due to Friedländer's bacillus treated with this new antibiotic. Although the issue was fatal, the initial prompt clinical and bacteriologic response to streptomycin confirms previous favorable reports of its use in other types of infection due to this organism.

CASE REPORT

A sixty year old negress was admitted to the New Haven Hospital on November 12, 1946, with complaints of fever, chills, abdominal pain, vomiting and diarrhea. Except for symptoms of intolerance to fatty and greasy foods characterized by nausea and eructation, the patient had enjoyed good health until the present illness.

Two days before admission she suddenly felt chilly and shortly thereafter developed severe abdominal pain. This was at first localized to the epigastric region and to the right upper

quadrant but later radiated through to the back. She became nauseated and vomited large amounts of liquid material which was not grossly bloody. She passed watery stools at frequent intervals. Her family physician reported temperatures of 104°F. on the first and second days, and there were at least two shaking chills during this time.

Except for headache and prostration, there were no other symptoms of consequence. She became progressively worse and was admitted to the hospital late in the night of the third day of her illness.

On admission the patient looked acutely and desperately ill. She was enormously obese and obviously suffered extreme abdominal pain. The temperature was 102.4°F., pulse rate was 100, respiratory rate was 20 and blood pressure was 130/70. She was incontinent of feces and frequently passed dark brown, foul-smelling watery stools. The skin was warm and moist. There was no jaundice. Pupils were equal and reacted to light. There were no signs of meningitis. The thyroid was diffusely enlarged. No adenopathy could be found. The heart was not remarkable. There were a few medium, moist rales at both lung bases. Although the huge size of the abdomen made examination difficult, there was considerable generalized tenderness, with spasm in the right upper quadrant and under the right costal margin posteriorly. Pelvic and rectal examinations were considered negative.

Examination of the blood revealed a red cell count of 5,300,000 per mm.³ and a hemoglobin of 13.0 Gm. per cent. Leukocytes were 16,500 per mm.³ The differential showed 92 per cent neutrophils (26 per cent of which were non-segmented forms), 6 per cent lymphocytes and 2 per cent monocytes. The urine was cloudy

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and amber, with an acid reaction; specific gravity, 1.010; albumin reaction, 3 plus and sugar, negative. Microscopic examination of the centrifuged sediment revealed 1 to 3 red cells and 20 white cells per high power field.

A fresh stool was described as a dark brown liquid with a 3 plus guaiac reaction. Microscopic examination revealed a moderate number of white cells but no cysts or parasites.

In view of the basilar pulmonary moisture, determinations of venous pressure and circulation time (arm to tongue with calcium gluconate) were performed; the values were 10 mm. saline and 17 seconds respectively. X-ray of the chest revealed a clear pulmonary parenchyma and a normal cardiac silhouette. X-ray of the abdomen revealed only hypertrophic osteo-arthritis of the lumbar spine. There was no significant dilatation of the intestinal loops, and neither abnormal soft tissue masses nor radio-opaque shadows in the region of the gallbladder were apparent.

Cultures of the blood, nasopharynx, urine, and stool were planted and the patient was given a slow venoclysis of 1,500 cc. of normal saline and 1,500 cc. of 10 per cent glucose solution. In the morning her temperature was 103.0°F. and there was no change in her general condition. The blood non-protein nitrogen was 78 mg. per cent, serum CO₂ content was 22.5 mEq. per liter and serum chloride was 92.7 mEq. per liter. Agglutination tests with *Bacillus typhosus* and *B. paratyphosus* A and B antigens were carried out and were subsequently reported negative. Although the Mazzini reaction was positive, the Kahn and Wassermann tests were negative.

At this time the blood culture drawn on admission was found to be strongly positive. In addition to growth in the broth the plate count showed about 1,300 colonies per cc. of a short, thick, gram-negative encapsulated bacillus. The surface colonies were smooth, greyish-white and mucoid in appearance. Nose, throat, urine and stool cultures revealed the presence of a similar-appearing organism.

The patient's grave condition made it imperative to begin chemotherapy without waiting for further identification of the pathogen. Another blood culture was taken and a rapid infusion of 500 cc. of normal saline containing 5.0 Gm. of sodium sulfadiazine was administered. Four hours later the patient had a shaking chill and her temperature rose to 105.8°F. Another blood

culture was obtained shortly after the chill. The blood sulfadiazine level was 8.8 mg. per cent at this time. The patient became semicomatose and was incontinent of urine and feces. For the first time her neck was noted to be slightly stiff. Lumbar puncture yielded turbid fluid under an initial pressure of 300 mm. spinal fluid. It contained 700 white cells per cu. mm., 90 per cent of which were polymorphonuclear leukocytes. The total protein concentration was 117 mg. per cent. The sediment was loaded with what appeared to be the same organism previously seen in all the cultures.

By this time the organism in the first blood culture had been identified as Friedländer's bacillus, type B, by means of a positive quellung reaction with type-specific antiserum. In view of this sulfadiazine therapy was discontinued and the patient was started on streptomycin. A blood culture taken at this time revealed approximately the same number of organisms present prior to administration of sulfadiazine. One-half Gm. of streptomycin was administered intramuscularly every four hours and 50 mg. was injected intrathecally after removal of an appropriate amount of cerebrospinal fluid. Intramuscular injection of ½ Gm. every four hours, plus a daily intrathecal injection of 50 mg. was continued for the remainder of her brief course.

Figure 1 indicates the patient's subsequent progress. To be noted particularly are the rapid fall in temperature and the striking effect on the bacteriologic findings. Thirty-six hours after streptomycin had been started the temperature was normal and the patient appeared much better. After the initial intrathecal dose culture of the cerebrospinal fluid was sterile although a few organisms were seen on smear. On the following day both smear and culture were negative for the organisms and the last two samples of blood, drawn forty-eight and sixty hours after the start of streptomycin, were sterile.

Despite her clinical improvement, however, the patient's non-protein nitrogen continued to rise and she developed a mild acidosis. On the last day of life her CO₂ content was 17.4 mEq. per liter and the non-protein nitrogen was 119 mg. per cent. Urine output was adequate.

On the morning of the sixth day of the disease the patient had another shaking chill and her temperature rose rapidly to 104.2°F. She became comatose. The blood pressure dropped to 88/45.

There were no new physical signs. An infusion of 300 cc. of whole citrated blood, 500 cc. of plasma and 2,000 cc. of saline and glucose solution brought the blood pressure back up to previous levels. The patient remained comatose and expired late that night after developing signs of congestive heart failure.

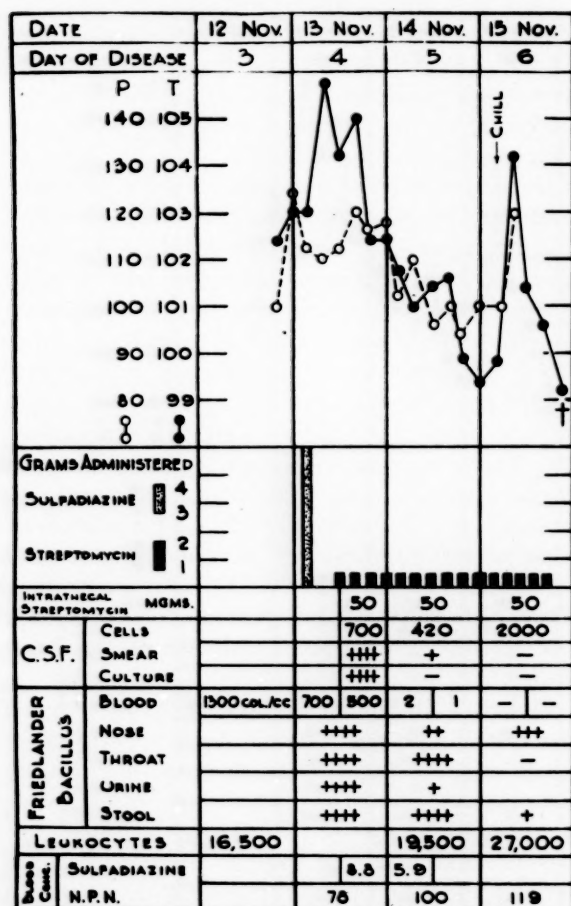


FIG. 1. Clinical and laboratory data in case of Friedländer's bacillus meningitis.

The stool cultures were of unusual interest. Initially they yielded a pure growth of an organism indistinguishable from Friedländer's type B bacillus isolated from the blood, cerebrospinal fluid, nose, throat and urine, except for the following points: (1) fermentation of dulcitate with the production of gas and acid, (2) a positive indol reaction and (3) the absence of capsular swelling with type specific A or B Friedländer's antiserum. Later cultures contained fewer of these organisms but there was a heavy growth of *Escherichia coli*. Biochemical reactions of the former organism are compared in Table I, with the organisms isolated from the

blood, spinal fluid, nose, throat and urine.* Table II summarizes the cultures made during the patient's life.

The organisms isolated from the other cultures all gave a positive reaction with type B Friedländer antiserum and exhibited most of the biochemical reactions usually attributed to Friedländer's bacillus. Streptomycin sensitivity determinations on the organism recovered from the blood on the third and sixth days of the disease showed that there was no significant change. The sensitivity at first was 16 micrograms per cc.; later it was 14 micrograms per cc.

Only those lesions found at autopsy and which are relevant to the last illness are described. Others are enumerated in the final anatomical diagnosis.

In the dome of the right lobe of the liver, lateral and posterior to the inferior vena cava, was a large abscess 10 cm. in diameter. There was a thin fibrous capsule from which friable fronds of tissue projected into thick pink-yellow pus. In the adjacent hepatic vein there was a large, flat, pink, adherent mural thrombus which narrowed the lumen of the vein only slightly. It reached within 1 cm. of the vena cava. Microscopically, the abscess wall was partly organized; the abscess contained necrotic liver tissue and pus as well as many Friedländer's bacilli. The thrombus was made up of fibrin, platelets and leukocytes but no bacteria. The underlying vein wall was partly disorganized but not necrotic.

The gallbladder wall was thickened to an average of 3 mm.; the mucosa was granular and there were three large calculi in the lumen. Microscopically, there were some lymphocytes but no polymorphonuclear leukocytes in the wall. The bile ducts were not dilated and contained no calculi.

The right kidney weighed 305 Gm. There were small scars in the pyramids as well as diffuse interstitial edema and necrosis of tubular epithelium. The left kidney was shrunken and deformed, weighing 135 Gm. The upper two-thirds was fibrotic with blunting of the papillae and enlargement of the calyces. The main artery to this area was thick-walled but not occluded. Microscopically, a thyroid pattern of dilated tubules filled with colloid casts was associated with marked hyperplastic arteriosclerosis and

* The authors are indebted to Miss Eleanora Falco, Technical Assistant, Yale University School of Medicine for the studies carried out upon the isolated organisms.

TABLE I
BIOCHEMICAL REACTIONS OF THE ORGANISM ISOLATED FROM THE BLOOD, SPINAL FLUID,
NOSE, THROAT, URINE AND STOOL

	Blood	Spinal Fluid	Nose	Throat	Urine	Stool
Lactose.....	AG	AG	AG	AG	AG	AG
Dextrose.....	AG	AG	AG	AG	AG	AG
Sucrose.....	AG	AG	AG	AG	AG	AG
Maltose.....	AG	AG	AG	AG	AG	AG
Mannite.....	AG	AG	AG	AG	AG	AG
Xylose.....	AG	AG	AG	AG	AG	AG
Dulcitate.....	SLA	SLA	—	SLA	SLA	AG
Salicin.....	AG	AG	AG	AG	AG	AG
Litmus milk.....	A	A	A	A	A	A
Kligers.....	Slant: A Butt: AG	Slant: A Butt: AG	Slant: A Butt: AG	Slant: A Butt: AG	Slant: A Butt: AG	Slant: A Butt: AG
Indol.....	—	—	—	—	—	+
Methyl red.....	—	—	—	—	—	—
Voges-Proskauer.....	—	—	—	—	—	—

TABLE II
SUMMARY OF BACTERIOLOGIC FINDINGS

Blood.....	11/12/46 (midnight) 11/13/46 (9 A.M.) 11/13/46 (1 P.M.) 11/14/46 (9 A.M.) 11/14/46 (5 P.M.) 11/15/46 (9 A.M.) 11/15/46 (5 P.M.)	1,300 colonies/cc. of Friedländer's bacillus, type B 700 colonies/cc. of Friedländer's bacillus, type B 500 colonies/cc. of Friedländer's bacillus, type B 2 colonies/cc. of Friedländer's bacillus, type B 1 colonies/cc. of Friedländer's bacillus, type B No growth No growth
Spinal fluid.....	11/13/46 11/14/46 11/15/46	Heavy growth, Friedländer's bacillus, type B No growth No growth
Nose.....	11/13/46 11/14/46 11/15/46	Heavy growth, Friedländer's bacillus, type B Light growth, Friedländer's bacillus, type B Moderate growth, Friedländer's bacillus, type B
Throat.....	11/13/46 11/14/46 11/15/46	Heavy growth, Friedländer's bacillus, type B Heavy growth, Friedländer's bacillus, type B; scant growth, <i>Staphylococcus albus</i> Moderate growth, <i>Staphylococcus albus</i>
Urine.....	11/13/46 11/14/46	Heavy growth, Friedländer's bacillus, type B Scant growth, Friedländer's bacillus, type B
Stool.....	11/13/46 11/14/46 11/15/46	* Heavy growth, Friedländer's bacillus * Heavy growth, Friedländer's bacillus; heavy growth, <i>E. coli</i> * Scant growth, Friedländer's bacillus; heavy growth, <i>E. coli</i>

* Type-specific serum failed to produce capsular swelling with this organism.

productive endarteritis as well as edema and round cell infiltration of the submucosa of the pelvis.

In the first part of the duodenum there was a small depressed scar made up of fibrous tissue and a few lymphocytes with an intact overlying mucosa. There was slight clouding of the meninges in the sulci over the cerebrum and around the base of the brain, reflected histologically by small accumulations of leukocytes. No gross or microscopic evidences of cerebritis or cerebral abscess were found. The spinal cord was not examined.

Postmortem cultures were reported as follows: Liver abscess, many colonies of Friedländer's bacillus; heart's blood, two colonies of Friedländer's bacillus per cc.; gallbladder bile, no growth.

Anatomic diagnoses were: Primary: Chronic cholecystitis and cholelithiasis; chronic pyelonephritis, bilateral; atrophy of the left kidney; hypertrophy of the right kidney; liver abscess, thrombus in the right hepatic vein;* acute meningitis; acute splenic tumor; pulmonary congestion; cloudy swelling of the viscera. Subsidiary: Syphilitic aortitis; mural thrombus of aorta; chronic aortic valvulitis; cardiac dilatation; myocardial scars; focal fibrosis of the lungs; fibrous pleural adhesions; hyperplasia of the thyroid gland; fibromyoma of the uterus; obesity.

The liver abscess was obviously older than the history had indicated. The original source of infection could have been the chronic pyelonephritis or more likely the chronic cholecystitis; less probably, the fibrous scars in the duodenum or lungs. It is also possible that an enteric focus which healed without residua was responsible, this ordinarily being the most common explanation for single pyogenic liver abscesses. The hepatic vein thrombus was doubtless the source of further dissemination of the organisms to the blood and meninges. No explanation of the sudden death after preliminary improvement was afforded by the autopsy, the syphilitic disease of the aortic valve and aorta being minimal.

COMMENTS

Based upon the summary of the thirty cases previously prepared by Ransmeier and Major¹ and the twenty-three cases

* Clinically, B. Friedländeri type B septicemia.

reported by others^{2-6,11-13,14} this case of meningitis due to Friedländer's bacillus brings the total of reported cases of this disease to 54. As previously noted and commented upon in greater detail further, meningitis due to *Aerobacter aerogenes* is also included in this group. Some pertinent facts about these cases are summarized in Table III.

The age distribution is of particular interest. Eleven instances were found in infants one year of age or less, three cases were found in the third year of life and, with the exception of two cases occurring between the ages of ten and nineteen, the remaining twenty-four cases for which exact age data are given fall in the group of those past twenty years of age.

Study of sex distribution brings out an apparent predilection of the disease for males. In forty-nine cases thirty-seven were stated to be males and twelve were females.

Analysis of the probable portal of entry of the organism into the blood stream and subsequently the subarachnoid space (although in some instances the subarachnoid space may have been entered primarily) does not indicate any essential difference between the infant and adult groups. The most common portal of entry would appear to be through penetrating wounds of the central nervous system or infections of the upper and lower respiratory systems. Otitis and mastoiditis are other common sources of infection. Less commonly the organism may invade through the gallbladder, the uterus or the urinary tract. In approximately one-fifth of the cases the portal of entry is not known or is not described.

In addition to the typical clinical findings of acute meningitis examination of the cerebrospinal fluid presents the picture of an acute purulent meningitis with cloudy, thick fluid under increased pressure. The cellular response is predominately polymorphonuclear in type, and smear and culture of the fluid for organisms of the Friedländer's—*Aerogenes* group are usually positive. For instance, in twenty-eight of the cases wherein note was made concern-

ing identification of organisms by smear, the smear was positive in twenty-three instances. Culture of the cerebrospinal fluid revealed the organisms in twenty-five of twenty-seven cases.

one of meningitis secondary to a unilateral mastoiditis and subdural abscess. The meningitis spontaneously subsided after drainage of the subdural abscess. Since then, reports have appeared describing

TABLE III
SUMMARY OF FIFTY-FOUR REPORTED CASES OF FRIEDLÄNDER'S BACILLUS MENINGITIS*

Age (in years)	0-1 11	6-9 0	40-49 3	Not stated exactly: 14
	1-2 0	10-19 2	50-59 5	
	2-3 3	20-29 5	60-69 2	
	4-5 0	30-39 6	70-79 3	
Sex	Male: 37	Female: 12	Not stated: 5	
Portal of Entry				
Focus	Age 3 or Less	Age over 3	Age Unknown	Total
Otitis, mastoiditis	1	7	0	8
Pneumonia, bronchitis	5	3	0	8
Paranasal sinuses	0	5	0	5
Cholecystitis	0	2	0	2
Uterine infection	0	2	0	2
Pharyngitis	0	1	0	1
Arthritis	1	0	0	1
Urinary tract	1	0	0	1
Wounds or operations on central nervous system	0	14	0	14
Other wounds	0	1	0	1
Unknown	6	3	2	11
	14	38	2	54

Bacteriology—Blood (antemortem): Culture positive in 12 of 18 cases

Cerebrospinal fluid: Smear positive in 23 of 28 cases; culture positive in 25 of 27 cases

Prognosis—Positive blood culture: All 12 patients died; negative blood culture: in 6 patients, 2 survived

* Published data incomplete for some of these patients.

In eighteen cases in which antemortem culture of the blood was performed such culture was positive in twelve instances. All of the patients in this group died. Of the remaining six patients with negative blood cultures two survived.^{8,9}

Only five survivals have been reported: the two patients with negative blood cultures just noted, and three additional cases recently reported by Mori,² Paine et al.⁶ and Montes¹¹ in which information was not given concerning blood culture.

Specific Therapy. Before the advent of chemotherapy, examination of the literature on Friedländer's bacillus and *A. aerogenes* meningitis revealed only one instance in which recovery took place. This case, reported by Rothschild⁷ in 1931, was

the treatment of this disease with sulfanilamide,¹ sulfapyridine⁸⁻¹⁰ sulfadiazine,³⁻⁴ penicillin and streptomycin separately or together^{2,5,6,12,13} and penicillin with sulfonamides.^{5,14} These reports further indicate that four recoveries have taken place following specific therapy: two cases with sulfapyridine,^{8,9} one case with sulfadiazine,³ and one case with streptomycin therapy.⁶

In addition to these four recoveries Tartakoff, Grynbaum and LeCompte² have described a patient treated with streptomycin; this treatment resulted in apparent bacteriologic cure although the patient eventually died of pulmonary embolism. To date a total of eight patients have been treated with streptomycin, with but one

recovery. In several instances the drug was not started until late in the course of the disease and may not have had a fair trial. In three of the patients no data on dosage are available. Analysis of the recovered patients reveals nothing of significance with respect to age, sex or portal of entry. However, it is of interest to point out again that not a single recovery has resulted from this type of meningitis in which the blood culture was initially reported to be positive. Results of blood culture were described in two of the recovered patients. In both instances the blood cultures were negative.

Streptomycin has a potent effect upon experimental infections caused by Friedländer's bacillus,¹⁵ and it has been reported as extremely effective in a variety of other infections in the Friedländer-Aerogenes group.¹³ It would appear that this new antibiotic may be the present treatment of choice for meningitis due to these organisms. A daily dose of 4.0 gm. administered intramuscularly at intervals of from four to six hours supplemented by an intrathecal administration of 50 mg. of the drug once a day may eradicate bacilli from the blood and cerebrospinal fluid.

Bacteriology. The differentiation of Friedländer's bacillus from *A. aerogenes* is extremely difficult and sometimes impossible. Occasionally one cannot even separate these organisms from *E. coli*.¹⁰ For clinical purposes it is necessary in the light of present knowledge to consider *B. Friedländer* and *A. aerogenes* in one group despite the fact that the former organism may be serologically divided into a number of types. The Friedländer-Aerogenes organisms are gram-negative bacilli with well defined capsules which produce luxuriant, raised, non-pigmented, mucoid and stringy colonies on solid media. They do not liquefy gelatin. Their biochemical reactions are exceedingly variable and even serologically identical strains may sometimes yield different tests.

These problems are well illustrated by the variable reactions of the organism isolated from our patient. (Table 1.) Although

capsular swelling was readily obtained by Friedländer type B antiserum with the strains isolated from the blood, cerebrospinal fluid, nose, throat and urine, such reaction could not be demonstrated with the organism isolated from the stool. Biochemical peculiarities such as indol production, dulcitate fermentation and methyl red reaction are presented in Table 1 for strains of the organism isolated from various body cavities.

SUMMARY

A fatal case of type B Friedländer's bacillus meningitis, septicemia, cholecystitis and liver abscess in a sixty year old female is reported. Although intramuscular and intrathecal therapy with streptomycin resulted in striking bacteriologic improvement, the patient suddenly died on the sixth day of the disease from an undetermined cause. This brings the total reported cases of Friedländer-Aerogenes meningitis to fifty-four. Before the advent of chemotherapy only one recovery was reported; since then, four additional recoveries have been reported in which the sulfonamides or streptomycin have been used.

Intramuscular and intrathecal administration of streptomycin is probably the treatment of choice although only one of several patients treated in this fashion has survived.

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Heart Block and Leukemic Cell Infiltration of Interventricular Septum of Heart*

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A CAREFUL review of the literature revealed only two instances of patients with leukemia who had 2:1 heart block^{1,2} and no reports of patients with leukemia and complete heart block. The paucity of literature on heart block in patients with leukemia and without other etiologic factors has prompted this report.

CASE REPORT

The patient was a forty-four year old, married, white, male carpenter who was admitted to Bellevue Hospital with the chief complaint of a sharp pain of five days duration which was aggravated by motion, shooting down the back of his left leg. His present illness began insidiously about six weeks before admission when he contracted a severe cold. Shortly thereafter he noticed that his gums were soft, sore and bled easily and that he tired more readily. Two weeks later he had "quinsy" sore throat which was treated by his local physician. At this time he began to have vague chest pains and exertional dyspnea which became progressively worse. The sciatic type of pain which brought the patient to the hospital began suddenly while he was lying in bed and it was so severe that he was unable to leave his bed. Two days prior to admission he became aware of some swelling of his ankles and hands. His past history was essentially negative except for gonorrhea at the age of nineteen and a rather indefinite history of asymptomatic hypertension for three or four years before his present illness. The family history was non-contributory.

Physical examination on admission showed a well developed and well nourished white man who appeared chronically ill. He was comfortable only when he lay still. His skin was pale and sallow. There was generalized subcutaneous edema, including the face, and small areas of

ecchymoses in the right axilla and on the posterior surface of the left arm. Conjunctivae were pale. Fundi showed recent hemorrhage and exudates. Gums were markedly hypertrophied, infected at tooth margins and crusted with blood. The tonsils were enlarged and there was a grayish ulceration at the lower pole of the right tonsil. There was generalized lymphadenopathy; none of the nodes, however, were larger than 3 to 5 mm. in diameter. There was a slight increase in the anteroposterior diameter of the chest. There were dullness, some suppression of breath sounds and a few medium moist rales at the base of left lung, posteriorly. The heart was slightly enlarged to the left; the place of maximum impulse was in the fifth interspace just lateral to the mid-clavicular line. Sounds were of fair quality. The heart action was regular, with a ventricular rate of 88 that was equal to the pulse rate. A grade II systolic murmur was heard over the precordium, loudest at the apex. P₂ was louder than A₂. The liver edge, firm, smooth and not tender, was felt two finger breadths below the costal margin. The spleen was not palpable. There was spasm of the low back muscles and great tenderness over the course of the left sciatic nerve. Any form of motion of the left hip elicited severe pain.

A provisional diagnosis of acute leukemia with leukemic infiltration or hemorrhage to involve the left sciatic nerve was made on admission.

Laboratory studies showed: hemoglobin, 6.5 Gm (Sahli); red blood cell count, 1.94 million; white blood cell count, 95,800 with 24 per cent neutrophils, 11 per cent lymphocytes, 2 per cent monocytes, 60 per cent "blasts," 3 per cent myelocytes; platelets 110,000. In spite of frequent transfusions the hemoglobin never was found to be higher than 9 Gm. and the red blood cells, 2.84 million. The differential count remained unchanged. Repeated urinalysis was

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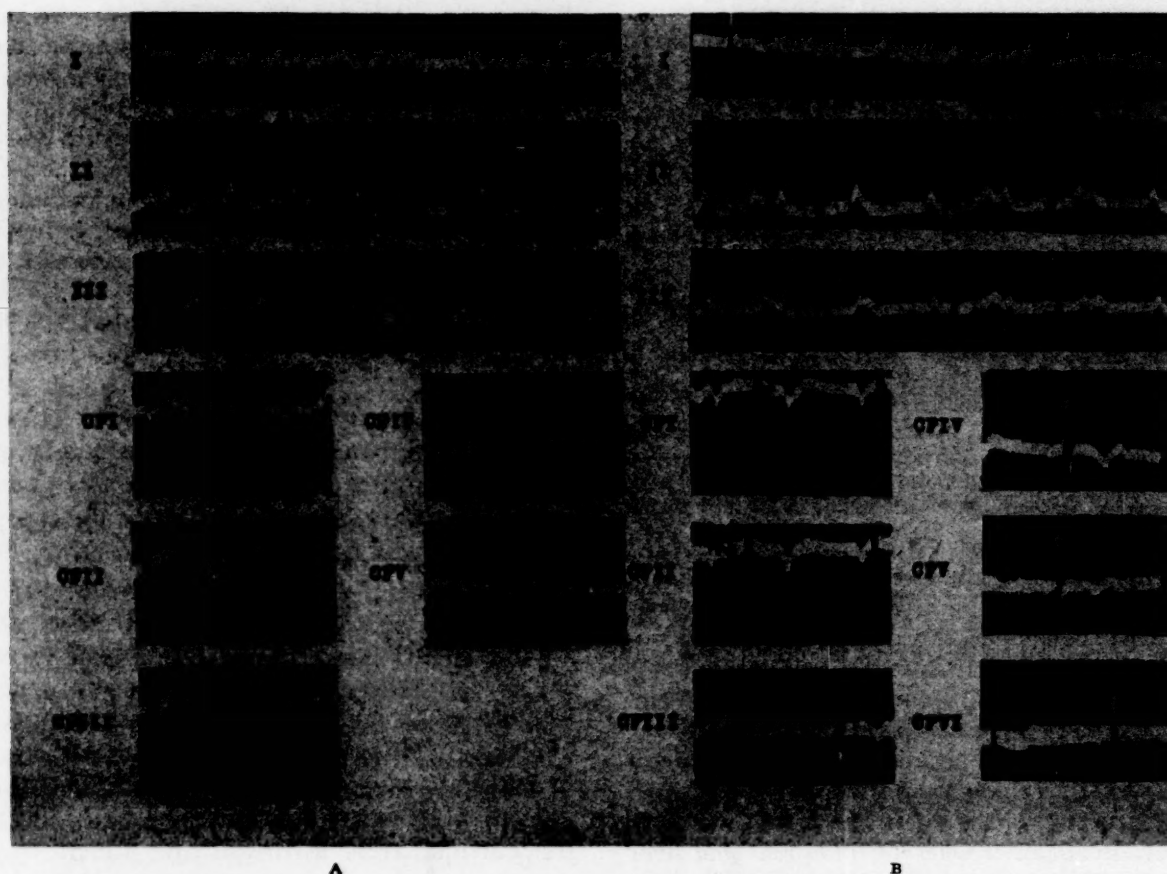


FIG. 1. Patient A. M. K. A, January 27, 1947; electrocardiogram six days after admission showing complete auriculoventricular dissociation. B, February 2, 1947; electrocardiogram six days later showing complete auriculoventricular dissociation and inversion of T waves in CF₁, II, III and IV.

negative except for one plus albumin and occasional white blood cells and granular casts in the sediment. Blood uric acid on three occasions was 3.7 mg. per cent, 6.2 mg. per cent and 7.5 mg. per cent, respectively. Serum proteins on two instances were 4.7 Gm. per cent (A/G = 1.1 Gm. per cent/3.6 Gm. per cent) and 5.7 Gm. per cent (A/G = 2.1 Gm. per cent/3.6 Gm. per cent). Electrocardiogram (Fig. 1A) on January 27, 1947, six days after admission, showed complete auriculoventricular dissociation, with an auricular rate of 100 per minute and a ventricular rate of 82 per minute. Duration of QRS equalled .08 second; electrocardiogram (Fig. 1A) repeated on February 2, 1947, continued to show complete auriculoventricular dissociation. The auricular rate was 94 per minute and the ventricular rate was 62 per minute. Duration of QRS equalled .10 second. The T waves showed progressive changes, now being deeply inverted in CF₁, CF₂, CF₃ and diphasic in CF₄ and CF₆.

APRIL, 1949

The patient's temperature fluctuated between 100 and 101°F. On the third hospital day the spleen could be felt at the left costal margin. The patient appeared to improve objectively as well as subjectively. The pain in his left hip and leg subsided at the end of the first week. Therapy consisted mainly of blood transfusions and penicillin. On the twenty-first hospital day the patient suddenly became apneic and gasped two to three times a minute; his pupils dilated widely and he appeared to be *in extremis*. Oxygen and artificial respiration were administered immediately and the patient regained consciousness, vomited and perspired profusely. Several hours after that episode he seemed to be his usual self. Two days later he was found dead in his bed.

The post-mortem findings (necropsy No. 35032) will be limited to those pertinent to this report. The heart weighed 400 Gm. The pericardium was smooth and glistening. All of the valves were delicate and competent. In places



FIG. 2. Photomicrograph of section of interventricular septum in the region just below the undefended space, showing leukemic cell infiltration, focal atrophy and fibrosis of the myocardium; hematoxylin and eosin, $\times 150$.

the myocardium appeared somewhat pale but there were no definite areas in the gross suggestive of leukemic infiltration. The left ventricular myocardium measured 1.7 cm.; the right ventricular myocardium measured 0.6 cm. The coronary ostia were patent and the coronary arteries contained occasional small cholesterol plaques. There was no narrowing or occlusion of the coronary arteries. In the aorta there were a few small atherosclerotic plaques. The liver weighed 2,750 Gm. and its lobular architecture was accentuated. The spleen weighed 630 Gm., was firm and the pulp was dark red. Several small infarcts were present. The right kidney weighed 250 Gm. and the left kidney weighed 300 Gm. There was diffuse, yellowish mottling throughout the cortex and medulla. The mesenteric lymph nodes were enlarged to 3 or 4 cm. in diameter and were firm and grayish-white on section. The remainder of the lymph nodes throughout the body varied in size from 0.5 cm. to 2 cm. in diameter and were similar in appearance to the mesenteric nodes. The bone marrow was dry and presented a pale grayish-pink surface. There were no other significant findings.

Several sections through the interventricular septum of the heart, particularly those beneath the undefended space, revealed both focal and diffuse areas of leukemic cell infiltration (myeloid series). (Fig. 2.) Wherever these cells were present there was some degree of atrophy of the myocardial fibers and, in places, fibrous tissue replacement. The remainder of the myocardium did not contain any leukemic cell infiltration and revealed no other unusual changes. The

liver, spleen, lymph nodes, bone marrow, lungs, intestinal tract, kidneys and gums were the sites of leukemic cell infiltration similar to that seen in the myocardium.

The final anatomic diagnosis was acute myeloid leukemia with involvement of lymph nodes, bone marrow, spleen, liver, lungs, alimentary tract, interventricular septum of heart, kidneys and gums; infarcts of spleen; atherosclerosis of aorta, minimal.

COMMENT

Of the two patients reported with leukemia and 2:1 heart block, demonstration of leukemic infiltration microscopically was possible in only one of them since necropsy permission was not granted in the other. It was assumed that leukemic infiltration of the septum was the underlying cause of the 2:1 heart block in the latter patient, a sixty-four year old white woman with long-standing hypertension who developed chronic myelogenous leukemia because the heart block was made to disappear for short periods after x-ray therapy was directed to the cardiac area. Aronson and Leroy,¹ in addition to the patient with the 2:1 heart block, presented seven other patients with leukemia in whom, microscopically, changes in the heart secondary to leukemia could be demonstrated. The changes consisted of one or a combination of the following: (1) leukemic infiltration in various layers of the heart, (2) engorgement of the capillaries with immature white cells, (3) recent small foci of interstitial hemorrhage and (4) severe fatty degeneration. Six of the eight subjects had manifested signs of heart disease and had abnormal electrocardiograms.

Leukemic infiltration of the myocardium is not an uncommon observation.²⁻⁵ Kirschbaum and Preuss,³ in going over 14,400 consecutive autopsies, found 123 cases of leukemia; of these, the heart was the second most commonly involved organ. They found leukemic cells in the capillaries and in the interstitial tissue between the myocardial fibers in forty-three (34 per cent) of the patients. Unfortunately, electrocardiographic studies were not reported in any

of these although seven of the cases were diagnosed clinically as either rheumatic or arteriosclerotic heart disease.

The reason for so few reports on heart block in patients with leukemia is not clear. It would seem that with the high percentage of cardiac involvement in leukemia, there should be more instances of heart block. Complete and 2:1 heart block could be overlooked on physical examination, especially in those cases in which there are normal pulse and ventricular rates. A ventricular rate of 70 to 90 with heart block in subjects who are anemic and/or febrile, as is frequent in patients with leukemia, would not be unusual. The patient in this report had a regular ventricular rate of 88 per minute on admission and a rate of 82 per minute as recorded by electrocardiogram six days later. The auriculoventricular dissociation was not suspected on admission and was discovered only after the electrocardiogram was taken. It is of interest to note that at the time of the second electrocardiogram, when the anemia had been improved somewhat by transfusions, the ventricular rate was 62 per minute, a rate suggestive of some degree of heart block. Perhaps routine electrocardiograms on patients with leukemia would demonstrate more instances of disturbance of the conduction mechanism as well as other abnormalities of the myocardium.

SUMMARY

A case report is presented, including post-mortem findings, of a patient with acute myeloid leukemia and heart block. There was no narrowing or occlusion of the coronary arteries.

Histologic examination of sections of interventricular septum of the heart revealed leukemic cell infiltration, focal atrophy and fibrosis of myocardium. The remainder of the myocardium was not involved in this process. The leukemic cell infiltration of the interventricular septum of the heart was probably the primary etiologic factor in the disturbance of the conduction mechanism.

It is suggested that perhaps routine electrocardiograms would reveal more instances of heart block in patients with leukemia since heart block in patients who are anemic and/or febrile may be overlooked on physical examination.

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Book Review

The Acute Bacterial Diseases—Their Diagnosis and Treatment. By Harry F. Dowling, M.D., with the collaboration of Lewis K. Sweet, M.D. and Harold L. Hirsh, M.D. P. 465, illustrated. Philadelphia, 1948. W. B. Saunders Company. Price \$6.50.

This new book presents a discussion of acute bacterial diseases "with the purpose of combining the new order of diagnosis and treatment with that which is worth while in the old order. It is intended as a practical guide for physicians and interested students."

The work is divided into four main sections: Part I comprises a brief outline of the general diagnostic features of acute bacterial infections, followed by an extended review of the nature, mode of action, indications for use and toxic effects of therapeutic agents, including serum, sulfonamides, penicillin and streptomycin. Parts II and III deal with individual diseases caused by cocci and bacilli. Part IV considers bacterial infections in which exotoxins are a major factor and closes with a short appendix in which methods are described for the assay of penicillin and streptomycin in body fluids and the determination of sulfonamide levels in blood and urine.

In general the subject matter is well presented but many sections, especially those dealing with the treatment of specific disease entities, appear to have been written some time ago without recent revision. The appraisal of the sulfonamide drugs is uncritical and proper emphasis is not placed on the marked differences in their bacteriostatic properties as, for example, between sulfanilamide and sulfadiazine. The schedules of treatment with penicillin recommended smaller doses than are usually employed at present and are definitely inadequate in some instances, notably in the initial therapy of subacute bacterial endocarditis. The oral administration of penicillin is also repeatedly advocated although this method is generally considered to be wasteful of penicillin and fraught with the dangers of variable destruction and absorption of the antibiotic.

Several errors were noted. The portion of the sulfonamides not bound to protein is stated to be inactive therapeutically.

Shock associated with infection is considered to be irreversible when it "has reached a severe stage, as evidenced especially by depression of the systolic and diastolic blood pressures." Influenza is included among the list of diseases to be differentiated in cases of long-standing fever. In addition to these lapses the reviewer takes issue with the authors regarding their views on the frequent development of resistance to penicillin by pneumococci and group A hemolytic streptococci. Moreover, the lurid description of the chronic stage of brucellosis is unsupported by specific references and resembles a dramatic account for the lay press rather than a considered opinion for the guidance of the physician and student.

These critical comments should not be constructed as impugning the value of the book as a whole. The authors are to be congratulated for a timely, concise, well planned account of their subject.

H.M.R.

It has been called to my attention that in the review entitled "Psychosomatic Medicine, Its History, Development and Teaching" by Dr. Bernard B. Raginsky of Montreal, Canada, which appeared in *The American Journal of Medicine*, in December, 1948, certain verbatim quotations were not properly acknowledged. These paragraphs on page 861, were taken from an article by Dr. Manuel D. Zane of New York entitled "Psychosomatic Considerations in Peptic Ulcers" which appeared in *Psychosomatic Medicine*, 9: 372-380, 1947.

The following statements are those in question:

"Most clinicians . . . accepted concepts in peptic ulcers."

"Many workers . . . consider as insurmountable."

"Although the underlying conflict . . . unobtrusive."

"In 1932 Cushing . . . pepsin-bearing glandular tissue."

"This concept affords . . . effective approach to them."

The editor regrets this oversight, which appears to have been unintentional, and offers his apologies to Dr. Zane and to the editors of "Psychosomatic Medicine."

ALEXANDER B. GUTMAN, M.D.



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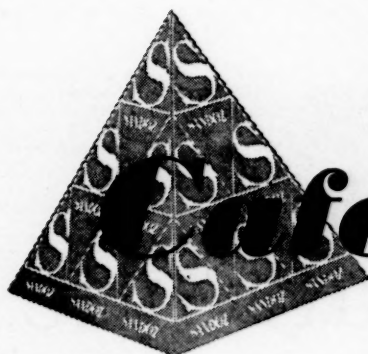
Later reports^{3,4} were equally favorable.

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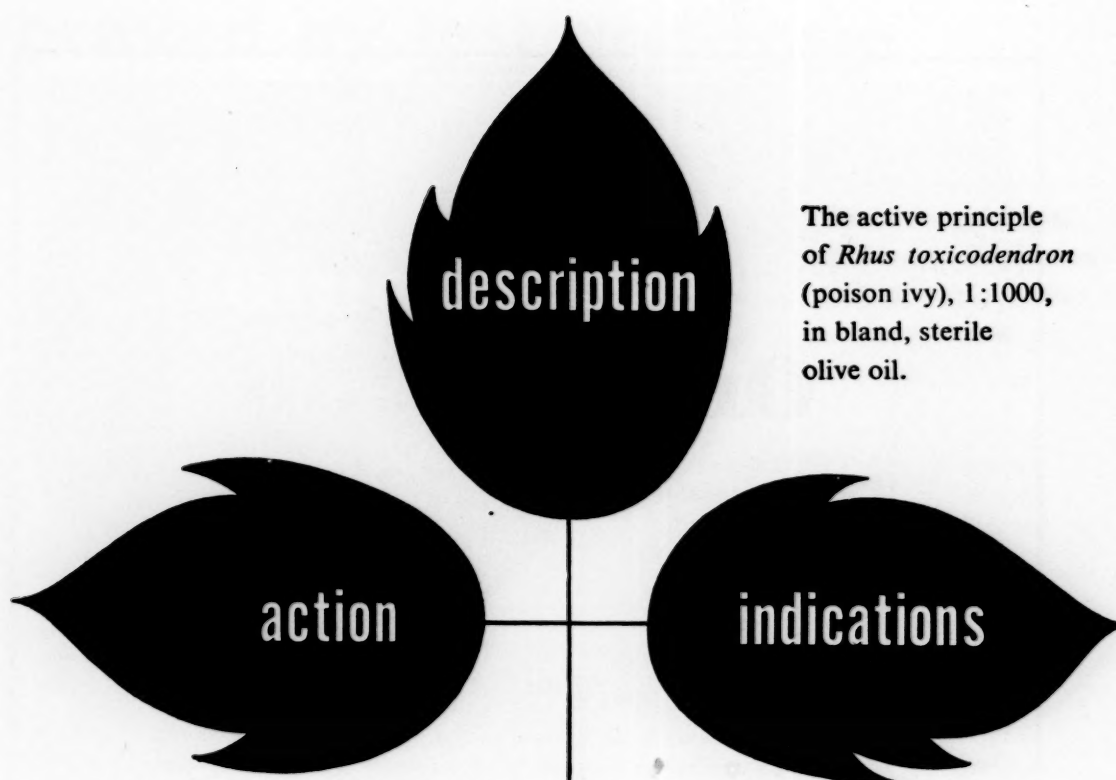
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REFERENCES:

1. J. Pediat. 32:1 (1948).
2. Am. J. M. Sc. 213:513 (1947).
3. J. Pediat. 32:119 (1948).
4. New England J. Med. 230:817 (1947).
5. New York State J. Med. 48:517 (1948).
6. Lancet 1:255 (1947).

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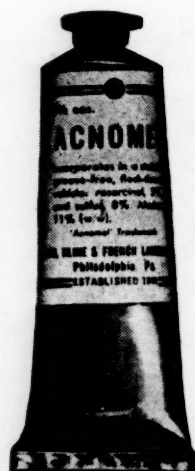
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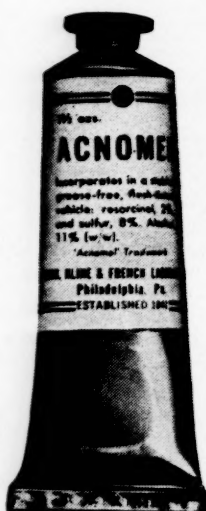
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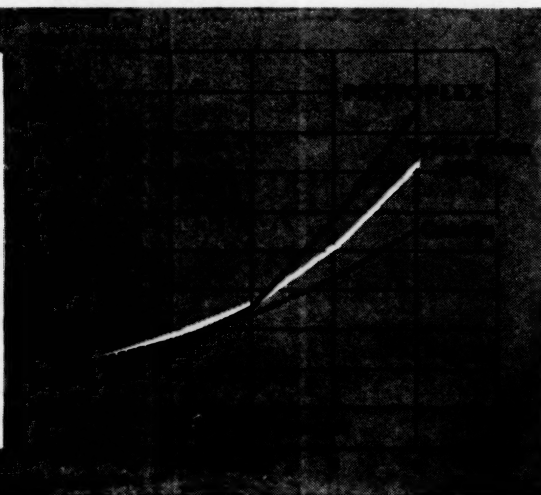
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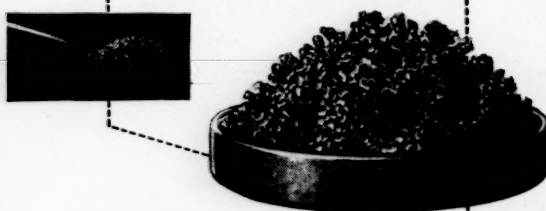
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*Gray, H. and Tainter, M. L.: Colloid Laxatives Available for
Clinical Use, Am. J. Dig. Dis. 8:130-139 (1941).

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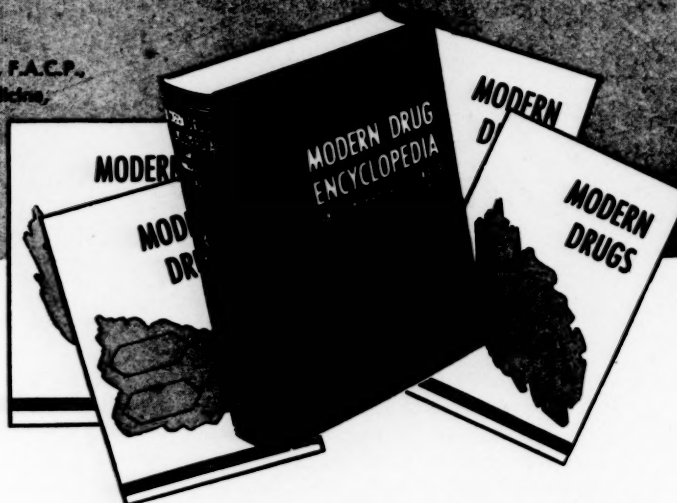
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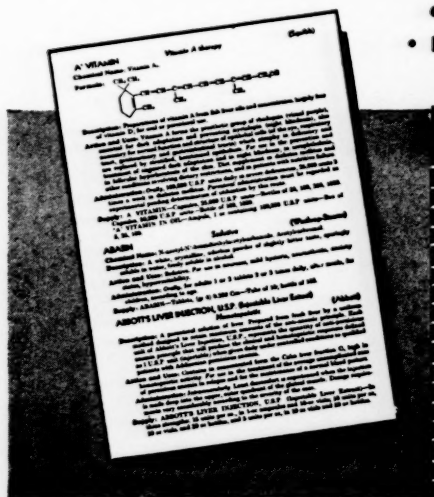
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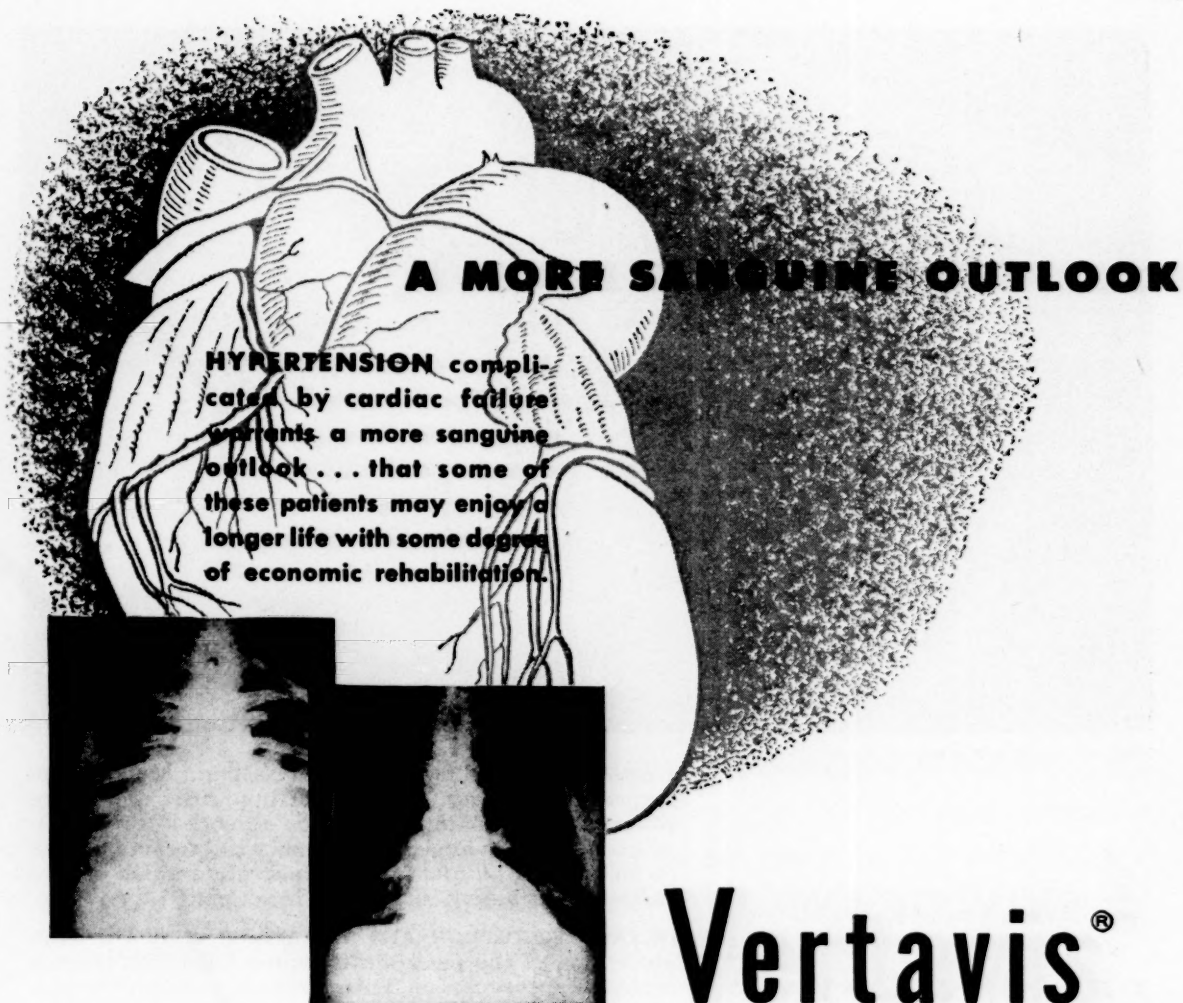
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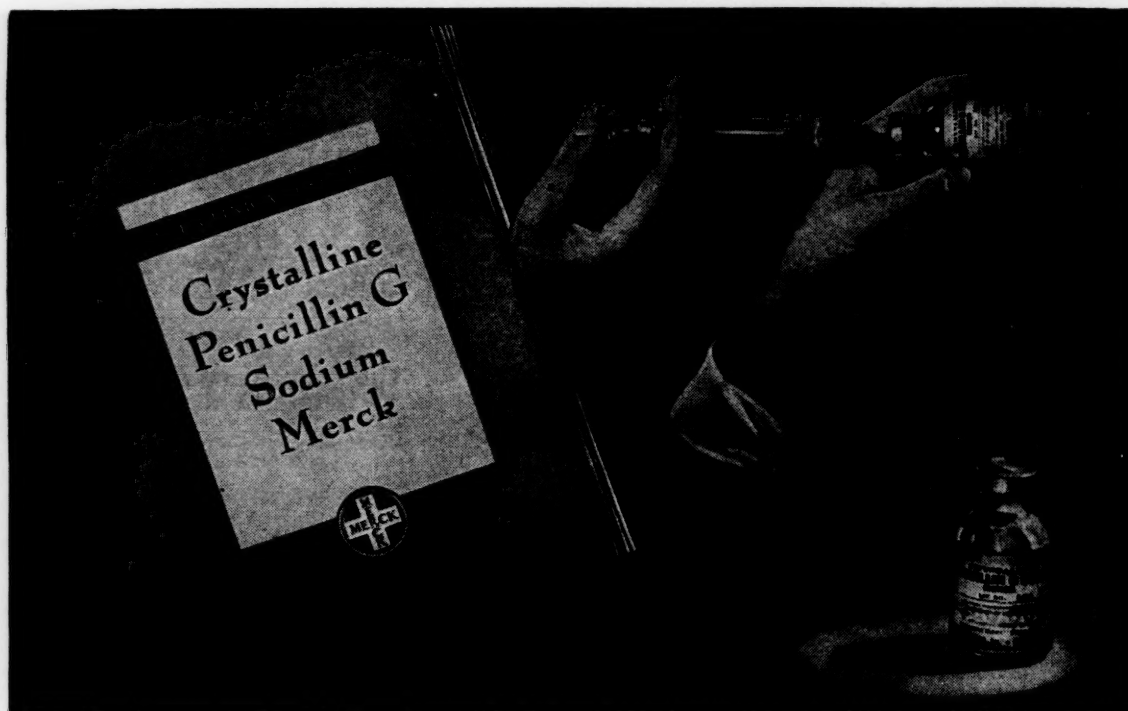
1. Freis, E. D., and Stanton, J. R.: Am. Heart J. 36:723-738, 1948.

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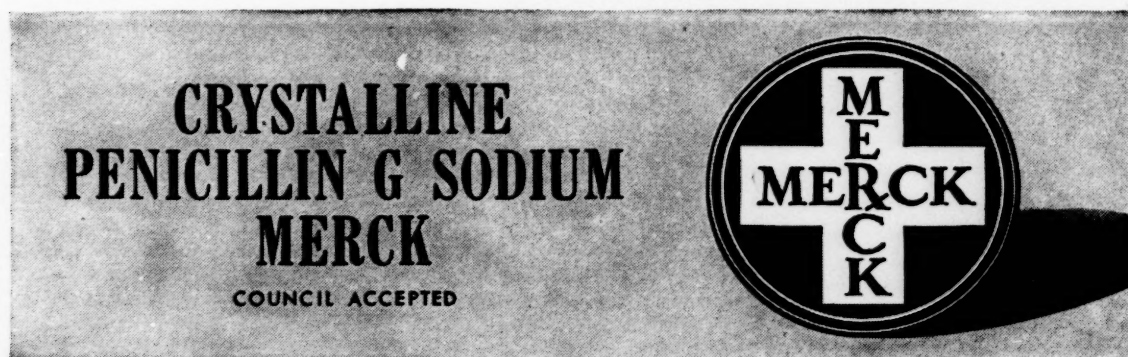
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¹Cannon, P. R.; Steffee, C. H.; Frazier, L. J.; Rowley, D. A., and Stepto, R. C.: The Influence of Time of Ingestion of Essential Amino Acids upon Utilization in Tissue Synthesis, *Fed. Proc.* 6:390, 1947.

²Geiger, E.: The Role of the Time Factor in Feeding Supplementary Proteins, *J. Nutrition* 36:813 (Dec. 10) 1948.

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